KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Genetic Screening and Testing

Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees (for in-network coverage).

Prevention and Invitae Corporation are the preferred labs for genetic testing, when the test(s) is/are available at Prevention or Invitae and medical necessity criteria are met.*

Invitae's test catalog can be found here: Invitae Test Catalog
Prevention test catalog can be found here: Prevention Test Catalog

**Note: This does not affect processing of tumor or other pathology specimens as they are not performed by Invitae*

PPO/POS members may use non-preferred labs at the out of network cost share.

Exceptions
For the genetic test(s) listed below, please use the lab specified/refer to the link attached:

- ***Cell Free Fetal DNA testing* – Any of these three labs can be used:**
  - *Ariosa (Bioreference) Diagnostics, Inc. (81507) or*
  - *Invitae (81420) or*
  - *LabCorp (81420)*
  - *Quest-QNatal (81420)*
- ***Next Generation Sequencing for Advanced Cancer*** —Any of these three labs can be used:
  - *CellNetix SymGene Panel*
  - *Oncoplex (University of Washington)*
  - *Caris Life Sciences*
- Prenatal Chromosomal Microarray (samples typically obtained via amniocentesis/CVS)—Either of these two labs can be used:
  - Prevention
  - LabCorp
- Fetal diagnostic testing in cases of recurrent intrauterine fetal demise (definition)—Either of these two labs can be used:
  - Prevention
  - LabCorp
- Carrier Screening for Preconception Counseling—Either of these two labs can be used:
  - Prevention
  - Invitae
- Non-prenatal Chromosomal Microarray (sample obtained by blood draw)—Any of these three labs can be used:
  - Prevention
  - LabCorp

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- Invitae

Related Policies:
Genetic Panel Testing
Pharmacogenomic Testing

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Next Generation Sequencing (NGS) (90.2) (Applies to diagnostic lab tests using NGS for somatic (acquired) and germline (inherited) breast and ovarian cancer.) Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R) ***FDA-approved Companion Diagnostic tests*** *(not all-inclusive)* FoundationFocus™ CDxBRCA Assay (Foundation Medicine, Inc.) FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.) Guardant360® CDx (Guardant Health, Inc.) Guardant360 TissueNext (Guardant Health, Inc.) Oncomine™ Dx Target Test (Thermo Fisher Scientific, Inc.) Praxis™ Extended RAS Panel (Illumina, Inc.) MSK-IMPACT™ (Memorial Sloan Kettering Cancer Center's (MSK) IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)) Chimeric Antigen Receptor (CAR) T-cell Therapy (110.24)
Local Coverage Determinations or Articles (LCD/LCA)	9/30/2015 - Noridian retired LCD for Genetic Testing (L24308). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an LCD. Most LCDs are not retired because they are incorrect. The criteria should be still referenced when making an initial decision. However, if the decision is appealed, the retired LCD cannot be specifically referenced. Maximus instead looks for "medical judgment" which could be based on our commercial criteria or literature search. MolDX: Molecular Diagnostic Tests (MDT) (L36256) MolDX: Testing of Multiple Genes (A58121) MolDX: Next-Generation Sequencing for Solid Tumors (L38121) (Applies to diagnostic lab tests using NGS for solid tumors.) MolDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis (L39469) Billing and Coding: MolDX: Next-Generation Sequencing for Solid Tumors (A57905) Billing and Coding: MolDX: Molecular Biomarker Testing to Guide Targeted Therapy Selection in Rheumatoid Arthritis (A59522)
Decision Memo	Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451)

General Coverage Rules – LCD 24308 (retired)

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1. Genetic tests for cancer are only a covered benefit for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e. clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Genetic testing is considered a non-covered screening test for patients unaffected by a relevant illness, injury, or signs/symptoms thereof.

2. Predictive or pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. For example, Medicare does not cover genetic tests based on family history alone.

3. A covered genetic test must be used to manage a patient. Medicare does not cover a genetic test for a clinically affected individual for purposes of family planning, disease risk assessment of other family members, when the treatment and surveillance of the beneficiary will not be affected, or in any other circumstance that does not directly affect the diagnosis or treatment of the beneficiary.

4. The results of the genetic test must potentially affect at least one of the management options considered by the referring physician in accordance with accepted standards of medical care (e.g. surgery, the extent of surgery, a change in surveillance, hormonal manipulation, or a change from standard therapeutic or adjuvant chemotherapy).

5. Pre-test genetic counseling must be provided by a qualified and appropriately trained practitioner.

6. An informed consent form signed by the patient prior to testing which includes a statement that he/she agree to post-test counseling is required. This consent form must be available on request by Medicare.

7. Genetic analysis must be provided through a laboratory which meets the American Society of Clinical Oncology (ASCO) recommended requirements:

The MolDX Program has determined certain gene tests do not meet Medicare's medical necessary requirements, and that the inclusion of these genes will result in an entire panel to be denied. MolDX has determined that testing for the below genes is a statutorily excluded service. Unless indicated otherwise, panels that include these genes will be denied. Please see the individual Test Coding and Billing Guidelines for each gene.

Palmetto GBA is the Medicare contractor for Molecular Diagnostic Testing – this site has the most up to date Medicare coverage guidelines for genetic testing.
MolDX® Program (Administered by Palmetto GBA)

Local Coverage Decisions and Articles (LCD/LCA) *not all-inclusive – refer to the MolDX® Program link above*

ID	Title	Codes *(not all-inclusive)*
L36163	08/20/2022 Noridian retired LCD MolDX: BRCA1 and BRCA2 Genetic Testing These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L36163 for determining medical necessity, along with L36256 MolDX: Molecular Diagnostic Tests (MDT).	81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81432, 81433, 0102U, 0103U, 0129U
L36386	MolDX: Breast Cancer Assay: Prosigna	81520
L37824	MolDX: Breast Cancer Index® Gene Expression Test	81518
L36186	MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease	81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339, 81450, 0027U, 0040U

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L36159	MolDX: Genetic Testing for Hypercoagulability / Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR)	81240, 81241, 81291
L36374	08/20/2022 Noridian retired LCD MolDX: Genetic Testing for Lynch Syndrome These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L36374 for determining medical necessity, along with L36256 MolDX: Molecular Diagnostic Tests (MDT).	81210, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, 81432, 81433, 0101U
L36192	MolDX: MGMT Promoter Methylation Analysis	81287
L36544	MolDX: HLA-DQB1*06:02 Testing for Narcolepsy (L36544) **not covered per LCD*	81383
L36256	MolDX: Molecular Diagnostic Tests (MDT)	See LCA*: Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) (A57527) **Presence of a code on this LCA does not indicate coverage*
L38333	MolDX: Blood Product Molecular Antigen Typing	0001U, 0084U
L36329	08/08/2022 Noridian retired LCD MolDX: ConfirmMDx Epigenetic Molecular Assay These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L36329 for determining medical necessity, along with L36256 MolDX: Molecular Diagnostic Tests (MDT)	81551
L38341	MolDX: Prostate Cancer Genomic Classifier Assay for Men with Localized Disease *(Decipher and similar, i.e., Prolaris)*	81541, 81542, 0047U
L36452	01/01/2018 Noridian retired LCD MolDX: Chromosome 1p/19q Deletion Analysis (L36452). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L36452 for determining medical necessity, along with L36256 MolDX: Molecular Diagnostic Tests (MDT).	
L36891	MolDX: Percepta© Bronchial Genomic Classifier	81479
L38329	MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer *(DetermaRx™)* Billing and Coding: MolDX: Predictive Classifiers for Early Stage	0288U

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L38816	MolDX: Minimal Residual Disease Testing for Cancer L38816 MolDX: Minimal Residual Disease Testing for Hematologic Cancers A58997 (refers to coverage for ClonoSEQ for specific cancers)	81479, 0340U, 0364U

For Non-Medicare Members

Members must meet **ALL the following** criteria:

1. The member is at clinical risk for a genetic condition because of current documented symptoms being displayed or a strong family history of the condition.
2. The test is scientifically valid and can be adequately interpreted.
3. The results will directly affect a member's clinical management or reproductive decisions.
4. After appropriate clinical work-up, and informed consent by the appropriate practitioner, the genetic test is indicated.

Genetic testing is not covered for the medical management of a family member who does not have Kaiser Permanente coverage.

Carrier Screening is limited to once per lifetime.

*For **specific tests listed** below the member must meet the criteria above **AND** the specific test criteria below:*

*For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access

Cardiology	Criteria
Arrhythmogenic Right Ventricular Cardiomyopathy – ARVC Genes	MCG* A-0627
Brugada Syndrome Channelopathy Genes	MCG* A-0594
Catecholaminergic Polymorphic Ventricular Tachycardia – Gene and Gene Panel Testing	MCG* A-0636
Coronary Artery Disease - 9p21 Allele	MCG* A-0657: This is not covered per MCG*
Coronary Artery Disease - KIF6 Gene	MCG* A-0656: This is not covered per MCG*
Coronary Artery Disease Genetic Panel	There is insufficient evidence in the published medical literature to show clinical utility.
Familial Dilated Cardiomyopathy – Gene and Gene Panel Testing	MCG* A-0648
Familial Hypertrophic Cardiomyopathy, Nonsyndromic – Gene and Gene Panel Testing	MCG* A-0633
Thoracic Aortic Aneurysm and Aortic Dissection (Hereditary) - Gene Panels	There is insufficient evidence in the published medical literature to show clinical utility.
Ehlers-Danlos Syndrome (Vascular) - COL3A1 Gene	MCG* A-0910
Loeys-Dietz Syndrome - Gene and Gene Panel Testing	MCG* A-0909
Long QT Syndrome (Hereditary) - Gene Panel	MCG* A-0918

Endocrinology	Criteria
Diabetes Mellitus, Type 2 - KCNJ11, KCNQ1, PPARG, SLC16A11 and TCF7L2 Genes	MCG* A-0826: This is not covered per MCG*

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Diabetes Mellitus (Maturity-Onset Diabetes of the Young) - ABCC8, APPL1, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4, and PDX1 Genes	MCG* A-0598

Gastroenterology	Criteria
HLA Testing for Celiac Disease:	1. Is medically appropriate for symptomatic patients a. Despite being on a gluten free diet **OR** b. With indeterminate serology/biopsy results 2. It is not covered for a. Asymptomatic people **OR** b. Screening
Hemochromatosis - HFE Gene	Medical necessity review no longer required.
Pancreatitis, Hereditary – CFTR, CPA1, CTRC, PRSS1, and SPINK1 Genes	MCG* A-0646

Genomic Testing Methods and Technologies	Criteria
Broad Spectrum Tumor Molecular Profiling – Next Generation Sequencing (NGS)	There is insufficient evidence in the published medical literature to show clinical utility.
Tacrolimus Pharmacogenetics - CYP3A4 and CYP3A5 Genes	MCG* A-0775: This is not covered per MCG*
Chromosomal Microarray Testing	1) Chromosomal microarray testing may be considered medically necessary for genetic evaluation of an individual when **ALL** of the following criteria are met: a) Testing has been requested following evaluation and genetic counseling by a medical geneticist, pediatric neurologist, or neurodevelopment pediatrician; and b) Results have the potential to affect clinical management of the patient; and c) The patient meets one or more of the following: • Multiple anomalies not specific to a well-delineated genetic syndrome • Apparently non-syndromic developmental delay/intellectual disability • Autism spectrum disorder • Dysmorphic facial features • Abnormal growth not otherwise explained 2) Chromosomal microarray testing (CPT 81228, 81229) may be considered medically necessary for patients undergoing invasive prenatal genetic testing (i.e., amniocentesis, chorionic villus sampling (CVS), or fetal tissue sampling), or a patient who has had recurrent (two or more) intrauterine fetal demise. Genetic counseling is required. Prior authorization is not required if done at Invitae, Labcorp or Prevention but is required for all other vendors in advance of submitting a claim for payment. 3) Chromosomal microarray testing may be considered medically necessary for testing of one or both parents when a chromosomal deletion or duplication has been identified in one or more of their offspring and: a. Parental testing is necessary to guide a

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Genomic Testing Methods and Technologies	Criteria
	reproductive decision, or b. Parental testing is necessary to determine the clinical significance of the chromosome abnormality found in the child, and c. The result is expected to directly affect clinical management of the child The following are not covered: 4) Chromosomal microarray testing to confirm the diagnosis of a disorder or syndrome that is routinely diagnosed based on clinical evaluation alone.
Genome-Wide Association Studies	Does not require medical review
MicroRNA Detection - Cancer	There is insufficient evidence in the published medical literature to show clinical utility.
MicroRNA Detection – Heart Failure	There is insufficient evidence in the published medical literature to show clinical utility.
MicroRNA Detection - Inflammatory Bowel Disease	There is insufficient evidence in the published medical literature to show clinical utility.
MicroRNA Detection - Ischemic Heart Disease	There is insufficient evidence in the published medical literature to show clinical utility.
MicroRNA Detection – Kidney Disease	There is insufficient evidence in the published medical literature to show clinical utility.
Molecular Profiling	MCG* A-0789: This is not covered per MCG*
Noninvasive Prenatal Testing (Cell-Free Fetal DNA) - Microdeletion Syndromes *81331 not medically necessary when performed using cell-free fetal DNA, 81422*	MCG* A-0848: This is not covered per MCG*
Noninvasive Prenatal Testing (Cell-Free Fetal DNA) - Monogenic Disorders	MCG* A-0849: This is not covered per MCG*
Noninvasive Prenatal Testing (Cell-Free Fetal DNA) - Sex Chromosome Disorders	MCG* A-0850: This is not covered per MCG*
Septin 9 (SEPT9) DNA Methylation Testing	MCG* A-0706: This is not covered per MCG*
Telomere Analysis	MCG* A-0672: This is not covered per MCG*
Integrated Molecular Pathology Testing (Topographic Genotyping) - PathFinderTG	MCG* A-0632: This is not covered per MCG*
Whole Exome Sequencing (WES)	Whole exome sequencing (WES) is considered medically necessary for a phenotypically affected individual when **ALL** of the following criteria are met: 1. Individual has been evaluated by a board-certified medical geneticist (MD) or other board-certified physician specialist with specific expertise in the conditions and relevant genes for which testing is being considered 2. Results have the potential to directly impact clinical decision-making and clinical outcome for the patient 3. A genetic etiology is the most likely explanation for the phenotype as demonstrated by **EITHER** of the following: A. multiple abnormalities affecting unrelated organ systems OR B. **TWO** of the following criteria are met: a. abnormality affecting a single organ system b. significant intellectual disability, symptoms of a complex neurodevelopmental disorder (e.g. self-injurious behavior, reverse sleep-wake cycles), or severe neuropsychiatric condition (e.g. schizophrenia, bipolar disorder, Tourette syndrome)

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Genomic Testing Methods and Technologies	Criteria
	c. family history strongly implicating a genetic etiology d. period of unexplained developmental regression (unrelated to autism or epilepsy) e. dysmorphic facial features f. abnormal growth not otherwise explained 4. No other causative circumstances (e.g. environmental exposures, injury, infection) can explain symptoms 5. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available 6. The differential diagnosis list and/or phenotype warrant testing of multiple genes and ONE of the following: a. WES is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis b. WES results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing *All requests must be approved by a KP geneticist, regardless of whether they have seen the patient.*

Hematology	Criteria
Alpha Thalassemia - HBA1 and HBA2 Genes	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0808
Beta Thalassemia - HBB Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0815
Fetal and Neonatal Alloimmune Thrombocytopenia - Human Platelet Antigen (HPA) Genotyping	MCG* A-0793
Factor V Leiden Thrombophilia-F5 gene	Does not require medical review
Fanconi Anemia - FANC Genes and Gene Panel Testing	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0683
Hemoglobin C and E – HBB Gene	MCG* A-0604
Hyperhomocysteinemia - MTHFR Gene	MCG* A-0629
Post-Transfusion Purpura - Human Platelet Antigen (HPA) Genotyping	There is insufficient evidence in the published medical literature to show clinical utility.

Hematology	Criteria
Prothrombin Thrombophilia - F2 Gene	Does not require medical review
Sickle Cell Disease - HBB Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0864
Von Willebrand Disease-VWF Gene	MCG* A-0688

Metabolic and Developmental Disorders	Criteria
Angelman Syndrome - UBE3A Gene *Note: Guideline indications are related to tests performed using amniocentesis or chorionic villus sampling. Not medically necessary when performed using cell-free fetal DNA (see MCG A-0848).*	MCG* A-0708

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Metabolic and Developmental Disorders	Criteria
Ashkenazi Jewish Genetic Panel	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0592
Autism Spectrum Disorders – Gene Panels	MCG* A-0914 This is not covered per MCG*
Beckwith-Wiedemann Syndrome - CDKN1C Gene	MCG* A-0765
Bloom Syndrome - BLM Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0682
Canavan Disease - ASPA Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0595
Deafness and Hearing Loss, Nonsyndromic - Gene and Gene Panel Testing	MCG* A-0823
Deafness and Hearing Loss, Nonsyndromic - GJB2, MT-RNR1, MT-TS1, POU3F4, PRPS1, and SMPX Genes	There is insufficient evidence in the published medical literature to show clinical utility.
Developmental Delay - Gene Panels	MCG* A-0925 This is not covered per MCG*
Fragile X-Related Disorders-FMR1 Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0602
Fragile X-Associated Primary Ovarian Insufficiency - FMR1 Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Fragile X-Associated Tremor/Ataxia Syndrome - FMR1 Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Gaucher Disease - GBA Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0603
Glycogen Storage Disease, Type 1 G6PC and SLC37A4 Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Intellectual Disability - Gene Panels	MCG* A-0923 This is not covered per MCG*
Joubert Syndrome – Gene Testing and Gene Panels	MCG* A-0785
Lesch-Nyhan Syndrome - HPRT1 Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Maple Syrup Urine Disease, Type 1 or Type 2 – BCKDHA, BCKDHB, and DBT Genes	MCG* A-0681
Maple Syrup Urine Disease, Type 3 - DLD Gene	MCG* A-0776
Mucolipidosis IV - MCOLN1 Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0686
Niemann-Pick Disease (Acid Sphingomyelinase Deficiency) - NPC1, NPC2, and SMPD1 Genes	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0611
Noonan Syndrome – Gene and Gene Panel Testing	MCG* A-0915
Prader-Willi Syndrome DNA Methylation Testing *Note: Guideline indications are related to tests performed using amniocentesis or chorionic villus sampling. Not medically necessary when performed using cell-free fetal DNA (see MCG A-0848).*	MCG* A-0707
Rett Syndrome – CDKL5, FOXG1 and MECP2 Genes	MCG* A-0687
Tay-Sachs Disease and Variants - HEXA Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0614
Usher Syndrome - ADGRV1 (GPR98), CDH23, CIB2, CLRN1, DFNB31, HARS, MYO7A, PCDH15, USH1C, USH1G, and USH2A Genes	MCG* A-0802
Fabry Disease - GLA Gene	MCG* A-0916

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Miscellaneous	Criteria
Autosomal and X-Linked Recessive Disease Carrier Screening - Expanded Gene Panels	MCG* A-0768: This is not covered per MCG*
Familial Mediterranean Fever - MEFV Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Hereditary Hemorrhagic Telangiectasia - ACVRL1, ENG, GDF2, and SMAD4 Genes	MCG* A-0704
Male Infertility - Y Chromosome Microdeletion Analysis	There is insufficient evidence in the published medical literature to show clinical utility.
Malignant Hyperthermia Susceptibility - CACNA1S and RYR1 Genes	There is insufficient evidence in the published medical literature to show clinical utility.

Nephrology	Criteria
Donor-derived cell-free DNA testing (e.g., Allosure)	*Please see separate criteria for **Donor-derived cell-free DNA testing for Kidney Transplant Rejection (e.g., AlloSure)**
Polycystic Kidney Disease (Autosomal Recessive) – DZIP1L and PKHD1 Genes and Gene Panels	There is insufficient evidence in the published medical literature to show clinical utility.

Neurology	Criteria
Alzheimer Disease – (Early Onset) APP, PSEN1, and PSEN2 Genes	MCG* A-0590
Alzheimer Disease (Late Onset) - APOE Genotyping	MCG* A-0809: This is not covered per MCG*
Amyotrophic Lateral Sclerosis (ALS) - SOD1 Gene	No additional criteria need to be met beyond numbers 1 - 4 at the top of the Non-Medicare criteria (page 4).
Ataxia-Telangiectasia - ATM Gene	MCG* A-0593
CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) - NOTCH3 Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Charcot-Marie-Tooth Hereditary Neuropathy – Gene and Gene Panel Testing	MCG* A-0691
Epilepsies (Hereditary) - Gene Panels	MCG* A-0905 This is not covered per MCG
Epilepsies, Hereditary - SCN1A Gene	MCG* A-0904
Familial Dysautonomia - ELP1 Gene	Does not require medical review in the prenatal setting. For all other indications refer to MCG* A-0685
Familial Frontotemporal Dementia - C9orf72, GRN, and MAPT Genes	There is insufficient evidence in the published medical literature to show clinical utility.
Friedreich Ataxia - FXN Gene	MCG* A-0907
Huntington Disease - HTT Gene	MCG* A-0605
Muscular Dystrophies (Duchenne, Becker) - DMD Gene	MCG* A-0608
Myotonic Dystrophy – Type 1 - DMPK Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Myotonic Dystrophy, Type 2 - CNBP Gene	There is insufficient evidence in the published medical literature to show clinical utility.
Narcolepsy - HLA Testing	MCG* A-1005 This is not covered per MCG
Nemaline Myopathy – Gene and Gene Panel Testing	MCG* A-0792
Parkinson Disease – Gene Testing and Gene Panels	MCG* A-0671 This is not covered per MCG

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Neurology	Criteria
Spinal Muscular Atrophy - SMN1 and SMN2 Genes **Spinal Muscular Atrophy – Carrier Testing** References: American College of Obstetricians and Gynecologists (2017). Carrier screening for genetic conditions. Committee Opinion No. 691. *Obstet Gynecol. 129*:e41-45. Retrieved 10/20/21 from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions Gregg, A. R., Aarabi, M., Klugman, S., Leach, N. T., Bashford, M. T., Goldwaser, T., Chen, E., Sparks, T. N., Reddi, H. V., Rajkovic, A., & Dungan, J. S. (2021). Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine, 23*(10), 1793–1806. Retrieved 10/20/21 from: https://doi.org/10.1038/s41436-021-01203-z	Preconception or prenatal carrier testing for spinal muscular atrophy (SMA) with analysis of the SMN1 gene (CPT code **81329**), as described by the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG), is considered medically necessary for a prospective biologic parent with the capacity and intention to reproduce. Testing is covered once in a lifetime. Kaiser Permanente will cover carrier testing for SMA (CPT 81329) without prior authorization when performed at a Kaiser Permanente lab, Invitae, or Prevention. Prior authorization will still be required for SMA carrier testing at any other lab in advance of submitting a claim for payment. All other spinal muscular atrophy genetic testing: Medical necessity review will be required for all other indications for SMN1/SMN2 gene testing using MCG* **KP**-0659. *Note – this is a KP hybrid, not MCG A-0659* (Includes CPT codes: 81336, 81337, 0236U)
Spinocerebellar Ataxia - Gene Testing and Gene Panels	MCG* A-0908
Transthyretin Amyloidosis - TTR Gene	There is insufficient evidence in the published medical literature to show clinical utility.

Oncology	Criteria
Acute Lymphoblastic Leukemia - BCR-ABL1 Fusion Gene Testing	Does not require medical review
Acute Promyelocytic Leukemia - PML-RARA Fusion Gene Testing	Does not require medical review
Breast Cancer - HER2 Testing	MCG* A-0766
Breast Cancer Gene Expression Assays CPT - 81519	See Oncotype Dx
Breast Cancer - PALB2 Gene	MCG* A-0989
Breast or Ovarian Cancer, Hereditary - BRCA1 and BRCA2 Genes CPT 81211, 81212, 81213, 81162	MCG* A-0499
Cancer of Unknown Primary: Gene Expression Profiling – 81540; CancerTYPE ID	MCG* A-0673 This is not covered per MCG
Chronic Eosinophilic Leukemia/Hypereosinophilic Syndrome - FIP1L1-PDGFRA Fusion Gene Testing	MCG* A-0770
Chronic Myelogenous Leukemia - BCR-ABL1 Fusion Gene Testing	Does not require medical review
ClonoSEQ – 0364U	ClonoSEQ is a new test whose current use is confined to clinical trials. It is not currently covered by KPWA
Cologuard	See Fecal DNA Testing
Colon Cancer - Oncotype DX	MCG* A-0651: This is not covered per MCG*
Colon Cancer Gene Expression Assay - GeneFx Colon	MCG* A-0821: This is not covered per MCG*

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Oncology	Criteria
Colorectal Cancer (Hereditary) – Gene Panel	MCG* A-0774: This is not covered per MCG*
Cowden Syndrome - PTEN Gene	MCG* A-0585
DecisionDx - Choroidal/Uveal Melanoma	DecisionDX is covered for dx of choroidal/uveal melanoma
DecisionDx - Cutaneous Melanoma	There is insufficient evidence in the published medical literature to show clinical utility.
Familial Adenomatous Polyposis - APC Gene	MCG* A-0534
Gastric Cancer, Hereditary - CDH1 Gene	MCG* A-0779
Gastrointestinal Stromal Tumor (GIST) - KIT and PDGFRA Genes	Does not require medical review
Ovarian Cancer (Hereditary) - Gene and Gene Panel Testing	Criteria currently under revision to be completed by 9/1/2022. Send to MD for review.
Li-Fraumeni Syndrome - TP53 Gene	MCG* A-0584
Lymphoma - T-Cell Antigen Receptor (TCR) Gene Rearrangement Testing	Does not require medical review
Lynch Syndrome - BRAF V600, EPCAM, MLH1, MSH2, MSH6, and PMS2 Genes and Gene Panel	MCG* A-0533
Malignant Melanoma (Uveal), Hereditary - BAP1 Gene	MCG* A-0836: This is not covered per MCG*
Malignant Melanoma (Cutaneous) – BAP1, CDK4 and CDKN2A Genes	MCG* A-0601: This is not covered per MCG*
Melanoma (Cutaneous) - Gene Expression Profiling	MCG* A-0837: This is not covered per MCG*
Melanoma (Uveal) - Gene Expression Profiling	MCG* A-0670: This is not covered per MCG*
Multiple Endocrine Neoplasia (MEN) Syndrome, Type 2 - RET Gene	MCG* A-0842
Multiple Endocrine Neoplasia (MEN) Syndromes - MEN1 Gene	MCG* A-0582
MUTYH-Associated Polyposis - MUTYH Gene	MCG* A-0828
Myelodysplastic Syndromes (Somatic) - Gene Panels	MCG* A-0791: This is not covered per MCG*
Myeloproliferative Neoplasms - JAK2 Genes	Does not require medical review
Myeloproliferative Neoplasms - MPL Gene	Does not require medical review
Neuroblastoma - ALK, MYCN, and PHOX2B Genes and Gene Expression Profiling	MCG* A-0610
Neurofibromatosis - NF1 Gene	MCG* A-0581
Neurofibromatosis - NF2 Gene	MCG* A-0846
Non-Small Cell Lung Cancer – Gene Testing (Somatic or Therapeutic	MCG* A-0795 Includes indications for: Anaplastic Lymphoma Kinase (ALK) Fusion Gene Testing – medically necessary when indications met EGFR Gene Testing – medically necessary when indications met KRAS Gene Testing – not medically necessary for NSCLC per MCG*
OVA1- Assessment for Ovarian Cancer	There is insufficient evidence in the published medical literature to show clinical utility.
Pancreatic Cancer (Hereditary) -	MCG* A-0797

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<table>
<tr><th>Oncology</th><th>Criteria</th></tr>
<tr><td>Gene Panel</td><td></td></tr>
<tr><td>Paraganglioma-Pheochromocytoma (Hereditary) - Gene Testing and Gene Panel</td><td>MCG* A-0798</td></tr>
<tr><td>Peutz-Jeghers Syndrome - STK11 Gene</td><td>MCG* A-0799</td></tr>
<tr><td>Prostate Cancer - BRCA1 and BRCA2 Genes</td><td>MCG* A-0612</td></tr>
<tr><td>Prostate Cancer – ConfirmMDx (CPT Code 81551)</td><td>ConfirmMDx (81551) for men with prior negative biopsy when repeat biopsy is being considered, and the following criteria are met (must be ordered by treating urologist):

• The beneficiary would benefit from treatment of prostate cancer and has greater than 10-year life expectancy
• Previous biopsy within the past 12 months negative or atypical small acinar proliferation (ASAP)
• Meets Age/PSA per table below
• Serial testing not covered (this is a one-time test)
• Concurrent testing with multiple assays is not medically necessary

TABLE 1. Age-Specific PSA Thresholds for Referral to Urology
<table><tr><th>Age Range (years)</th><th>PSA Threshold</th></tr><tr><td>40-49</td><td>>2.5 ng/ml</td></tr><tr><td>50-59</td><td>>3.5 ng/ml</td></tr><tr><td>60-69</td><td>>4.5 ng/ml</td></tr><tr><td>≥70</td><td>>6.5 ng/ml</td></tr></table></td></tr>
<tr><td>Prostate Cancer (Hereditary) – Gene Panel</td><td>MCG* A-0854: This is not covered per MCG*</td></tr>
<tr><td>Prostate Cancer - PCA3 Gene</td><td>MCG* A-0855: This is not covered per MCG*</td></tr>
<tr><td>Prostate Cancer Gene Expression Testing - Decipher</td><td>MCG* A-0856: This is not covered per MCG*</td></tr>
<tr><td>Prostate Cancer Gene Expression Testing - Oncotype DX</td><td>MCG* A-0712: This is not covered per MCG*</td></tr>
<tr><td>Prostate Cancer Gene Expression Testing – Prolaris (CPT Code 81541)</td><td>Men with confirmed prostate cancer on biopsy may be covered for Prolaris if</td></tr>
</table>

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ALL the following indications are met (must be ordered by treating urologist):

a. Must meet NCCN category* **(one):**
   - low-risk
   - favorable intermediate-risk
   - unfavorable intermediate-risk

b. who have greater than 10 year life expectancy

c. Meet **ONE of the following**:
   - has not received treatment for prostate cancer and is a candidate for active surveillance **or** definitive therapy; or
   - has intermediate-risk prostate cancer when deciding whether to add androgen-deprivation therapy to radiation; or
   - is appropriate for conservative management and yet would be eligible for definitive therapy (radical prostatectomy (RP), radiation or brachytherapy), or;
   - is appropriate for radiation therapy and yet would be eligible for the addition of a brachytherapy boost, or;
   - is appropriate for radiation therapy with short-term ADT yet would be eligible for the use of long-term ADT, or;
   - is appropriate for radiation with standard ADT yet would be eligible for systemic therapy intensification using next generation androgen signaling inhibitors or chemotherapy

d. Patient has not had a prostatectomy (***The evidence is insufficient for or against the use of Prolaris test in patients with radical prostatectomy and it is not covered***)

- Very low risk patients should be considered active surveillance, Prolaris is unlikely to be helpful
- Serial testing is not covered (this is a one-time test)
- Concurrent testing with multiple assays is not medically necessary

*NCCN Initial Risk Stratification and Staging workup for Clinically Localized Disease (see Tables)

Initial Risk Stratification and Staging Workup for Clinically Localized Disease	
Risk Group **Clinical/Pathologic Features**	
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/ml • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g
Low	Has all of the following but does not qualify for very low risk: • cT1-cT2a • Grade Group 1 • PSA <10 ng/mL

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<table>
<tr><th>Oncology</th><th>Criteria</th></tr>
<tr><td></td><td>
<table>
<tr><td>Intermediate</td><td>Has all of the following:
No high-risk group features
No very-high-risk features
Has one or more intermediate risk factors (IRFs):
cT2b-cT2c
Grade Group 2 or 3
PSA 10-20 ng/mL</td><td>Favorable intermediate</td><td>Has all of the following:
1IRF
Grade Group 1 or 2
<50% biopsy cores positive (e.g., <6 of 12 cores)</td></tr>
<tr><td></td><td></td><td>Unfavorable intermediate</td><td>Has one ore more of the following:
2 or 3 IRFs
Grade Group 3
≥50% biopsy cores positive (e.g., ≥ 6 of 12 cores)</td></tr>
<tr><td>High</td><td colspan="3">Has no very-high-risk features and has exactly one high-risk feature:
cT3a OR
Grade Group 4 or Grade Group 5 OR
PSA >20 ng/mL</td></tr>
<tr><td>Very High</td><td colspan="3">Has at least one of the following:
cT3b-cT4
Primary Gleason pattern 5
2 or 3 high-risk features
>4 cores with Grade Group 4 or 5</td></tr>
</table>
<table>
<tr><th>Grade Group</th><th>Gleason Score</th><th>Gleason Pattern</th></tr>
<tr><td>1</td><td><6</td><td><3 + 3</td></tr>
<tr><td>2</td><td>7</td><td>3 + 4</td></tr>
<tr><td>3</td><td>7</td><td>4 + 3</td></tr>
<tr><td>4</td><td>8</td><td>4 + 4, 3 + 5, 5 + 3</td></tr>
<tr><td>5</td><td>9 or 10</td><td>4 + 5, 5 + 4, 5 + 5</td></tr>
</table>
*NCCN Initial Risk Stratification and Staging Workup for Clinically Localized Disease
</td></tr>
<tr><td>Prostate Cancer – SelectMDx (CPT code 0339U)</td><td>There is insufficient evidence in the published medical literature to show clinical utility.</td></tr>
<tr><td>Proteomics - Ovarian Cancer Biomarker Panel (ROMA)</td><td>MCG* A-0858: This is not covered per MCG*</td></tr>
<tr><td>Proteomics (VeriStrat)</td><td>Epidermal Growth Factor Receptor Testing is covered when:
1) Diagnosis of NSCLC</td></tr>
<tr><td>Renal Cancer (Hereditary) - Gene Panel</td><td>MCG* A-0801: Considered medically necessary if indications in MCG A-0801 are met.</td></tr>
<tr><td>Retinoblastoma - RB1 Gene</td><td>MCG* A-0586</td></tr>
<tr><td>Thyroid Nodule Gene Expression Testing</td><td>
<table>
<tr><th>Test</th><th>Criteria</th></tr>
<tr><td>Afirma 81546
Thyroseq 0026U</td><td>There is insufficient evidence in the published medical literature to show clinical utility.</td></tr>
</table>
</td></tr>
</table>

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Oncology	Criteria	
	ThyGeNEXT® Thyroid Oncogene Panel + ThyraMIR Thyroid miRNA Classifier (CPT Codes *0245U+0018U)*	Molecular profiling of thyroid nodules with indeterminate cytology for ThyGeNext/ThyraMIR is medically necessary when specific criteria are met: • Thyroid nodule gene expression testing may be indicated when **ALL** of the following are present: ○ Thyroid nodule, as indicated by **ALL** of the following: ▪ Diameter of 1 cm or greater on ultrasound ▪ Indeterminate cytology on fine needle aspirate, as indicated by **1 or more** of the following): • Atypia of undetermined significance (ie, Bethesda System for Reporting Thyroid Cytopathology category III) • Follicular lesion of undetermined significance (ie, Bethesda System for Reporting Thyroid Cytopathology category III) • Follicular neoplasm or suspicious for follicular neoplasm (ie, Bethesda System for Reporting Thyroid Cytopathology category IV, excluding Hurthle cell type)
Von Hippel-Lindau Syndrome - VHL Gene	MCG* A-0583	
Wilms Tumor - WT1	MCG* A-0615	

Ophthalmology	Criteria
Age-Related Macular Degeneration - Gene Panels	MCG* A-0913 This is not covered per MCG
Retinal Disorders - Gene Panels	There is insufficient evidence in the published medical literature to show clinical utility.
Retinal Dystrophy - RPE65 Gene	MCG* A-1011

Orthopedics	Criteria
Ankylosing Spondylitis - HLA-B27 Testing	MCG* A-0762
Osteogenesis Imperfecta - Gene and Gene Panel Testing	MCG* A-0796

Pulmonary	Criteria
Alpha-1 Antitrypsin Deficiency - SERPINA1 Gene Ambulatory Care > Genetic Medicine > Pulmonary >Alpha-1 Antitrypsin Deficiency - SERPINA1 Gene (A-1006)	MCG* **KP-**1006 *Note – this is a KP hybrid, not MCG A-1006*
Beta2-Agonist Pharmacogenetics- ADRB2 Gene	MCG* A-0763: This is not covered per MCG
Cystic Fibrosis-CFTR Gene and Mutation Panel:	Does not require medical review in the prenatal setting. For all other indications refer to MCG* **KP-**0597 *Note – this is a KP hybrid, not MCG A-0597*

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Pulmonary	Criteria
Cystic Fibrosis Carrier Testing	Preconception or prenatal carrier testing for cystic fibrosis (CF) with targeted mutation analysis of 23 CFTR mutations (CPT code 81220) as described by the American College of Medical Genetics (ACMG) is considered medically necessary for a prospective biologic parent with the capacity and intention to reproduce. Any testing beyond the 23 gene CFTR mutations recommended by ACMG will not be covered as its utility has not been established. Testing is covered only once in a lifetime. ACMG Guideline - Minimum Mutation Panel for Population-Based Carrier Screening Purposes CF 3.3.1.
Congenital Central Hypoventilation Syndrome - PHOX2B Gene	There is insufficient evidence in the published medical literature to show clinical utility.

Risk Prognosticator Test	Criteria
• BREVAGen™ • Fibroblast Growth Factor Receptor 3 (FGFR3) • OVA1™ Test for the Assessment of Suspected Ovarian Cancer	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long- term outcomes than current standard services/therapies.
• MammaPrint Test (Gene-Expression Profiling Test, 70-Gene Prognostic Signature)	Medically necessary when **ALL** of the following criteria are met: 1. The patient has ER-positive, HER2-negative breast cancer ***and*** 2. One to three lymph nodes are positive for metastasis ***and*** 3. The patient is at high clinical risk for recurrence ***and*** 4. Outcome of testing will guide decision making regarding adjuvant chemotherapy.

***MCG are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Any genetic counseling notes if applicable Results of prior genetic testing
- Last 6 months of specialist notes of that is being reviewed (i.e., neurological notes, medical oncology notes, cardiology notes)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Evidence and Source Documents

Afirma
Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Intellectual Disability
ConfirmMDx for Prostate Cancer (MDxHealth Inc.)
Prolaris for Prostate Cancer
DecisionDx- Melanoma
HLA Testing for Celiac Disease
Micro Array for Evaluation of Intellectual Disability
OVA1 for Assessment of Ovarian Cancer
Risk Prognosticator Tests

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SelectMDx for Prostate Cancer (MDxHealth Inc.)
Thyroid Nodule Gene Expression Testing (Afirma)
Whole Genome/Exome Sequencing for Developmental Delay (DD)/Intellectual Disability (ID)

Background

Genetic screening is used to identify the genetic disorders or the potential for transmission of genetic disorders in populations at risk for a particular genetic disorder. Genetic screening is only appropriate when the natural history of the disease is understood; the screening tests are valid and reliable; sensitivity, specificity, false-negative, and false-positive rates are acceptable; and effective therapy is available. A sufficient benefit must be derived from a screening program to justify its cost.

Medical Technology Assessment Committee (MTAC)

Afirma

BACKGROUND

Thyroid nodules are clinically identified in 5-7% of the population, and incidentally on ultrasonography in up to 50% of women and 20% of men over the age of 50. Thyroid nodules are typically benign, but 5-15% prove to be malignant. It is thus recommended that any identified nodule measuring one centimeter or more in diameter be diagnostically evaluated. Ultrasound-guided fine needle aspiration (FNA) biopsy is the most widely used method for clinical evaluation of a suspicious thyroid nodule. FNA is a safe and simple outpatient procedure that yields cellular material suitable for cytological analysis. It can identify approximately 50% of malignant nodules and 70% of benign nodules without the need to perform a diagnostic surgery. However, 15-30% of the biopsied nodules have indeterminate cytology and cannot be conclusively diagnosed by FNA biopsy alone. Most patients with indeterminate lesions or lesions suspicious for malignancy, according to the Bethesda classification* system, are referred to surgery for both diagnostic and therapeutic purposes. Surgery is the recommended and appropriate treatment for thyroid cancer, however 70-75% of the nodules with indeterminate FNA cytology are found to be benign on final surgical pathology. Thus, a large proportion of these patients may undergo unnecessary partial or complete thyroidectomy with its potential surgical complications and risk of long-term morbidity (Alexander 2012, Duick 2012, Walsh 2012, Ali 2013, Labourier 2015, Sacks 2016).

Molecular markers and assays have been investigated for their ability to preoperatively classify the indeterminate thyroid nodules. Each has its performance characteristics and diagnostic values. Ideally a molecular marker or panel of markers is accurate in differentiating benign from malignant in any lesion that is considered suspicious or indeterminate. Molecular tests should also be simple to use, reproducible by the different institutions/laboratories, and cost-effective.

Molecular genetic testing for cytologically indeterminate thyroid nodules fall in two approaches: the “rule in” and the “rule-out” disease approach. Tests that rule-in malignancy (such as BRAF, RAS mutations, RET/PTC and PAX8-PPAry) have high specificity and positive predictive values (PPVs) for malignancy by identifying specific mutations or gene rearrangements known to be present in thyroid cancer. However, they have limited sensitivity and negative predictive values (NPVs) and fail to detect as many as 30% of malignancies. Tests that rule-out the disease on the other hand, should have a high sensitivity and negative predictive value in order to exclude malignancy when the test results are benign. Because a majority of nodules with indeterminate cytology are found to be benign on surgical resection, a test that can preoperatively rule-out malignancy may spare a subset of these patient’s unnecessary diagnostic surgeries (Alexander 2012, Kouniavsky 2012, Ward 2013, Chaudhary 2016. Nishino 2016).

*2008 Bethesda classification system for thyroid cytology: Class I: Nondiagnostic or unsatisfactory, Class II. Benign, Class III: atypia or follicular lesion of undetermined significance (AUS/FLUS), Class IV: follicular neoplasm or suspicious for follicular neoplasm (FN), Class V: suspicious for malignancy (SUSP) and Class VI: malignant) (Kuo, 2016)

Afirma gene expression classifier (GEC) is a molecular test developed by Veracyte Inc. (San Francisco, CA) with the intention of reducing unnecessary diagnostic surgeries in patients with thyroid nodules with indeterminate FNA cytopathologic results. It represents the “rule-out” approach by preoperatively identifying the benign thyroid nodules and ruling-out malignancy. Afirma GEC uses a proprietary diagnostic algorithm that analyses the mRNA expression of 167 genes to identify the signature of benign thyroid nodules. 142 of the 167 genes are in the main classifier, and 25 genes filter out rare neoplasms. The selected gene profile is based on the gene expression identified from FNAs of surgically proven benign and malignant thyroid nodules. During the Afirma GEC test RNA is extracted from the FNA sample, amplified and hybridized to a custom microarray to examine for gene patterns. These are compared with the GEC proprietary panel, which molecularly classifies them as either ‘benign’ or ‘suspicious’. Insufficient RNA

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in the sample leads to 'no result' conclusion in approximately 10% of cases. Nodules with benign results, in addition to clinical judgement, are typically followed up clinically and ultrasonography, while those with suspicious results undergo diagnostic thyroid lobectomy with possible total thyroidectomy (Alexander 2012, Kim 2012, Ward 2013, Kuo 2016, Witt 2016).

Afirma GEC is a proprietary test commercially owned by Veracyte Corporation and is offered through a sole source, which is a Clinical Laboratory Improvement Amendments certified [CLIA] reference laboratory. During a routine FNA of a thyroid nodule, after the aspirates are obtained for cytopathologic examination, two more needle passes are obtained for Afirma analysis and immediately stored in a preservative. These are either 1. Sent to a Veracyte independent industry partner (Thyroid Cytopathology Partners [TCP], Austin, TX) that performs cytopathologic exam of the FNA sample, and only runs the Afirma test for indeterminate diagnoses on cytopathology, or 2. In Thyroid Cytopathology Medical centers designated as "Enabled centers" cytopathology is done in-house and specimens with indeterminate results based on the Bethesda criteria are sent for Afirma GEC testing. Afirma test is run only on nodules with indeterminate cytology. If the cytopathologic evaluation reveals any other diagnosis or is nondiagnostic due to insufficient FNA samples, the preserved samples are discarded. The goal of the test is to identify the benign nodules from among those with indeterminate cytopathology. It is not intended to assist with clinical decision making for patients who have an indication for surgery or meet criteria for surgical interventions (Alexander 2012, Duick 2012, Ward 2013, Kuo 2016. Yip 2016).

03/20/2017: MTAC REVIEW

Evidence Conclusion: Analytic validity of Afirma GEC (From an earlier MTAC review)
Evaluating the analytic performance of Afirma GEC includes studying the stability of RNA in FNAs during collection, storage, and shipment; reproducibility of the test; and its analytic sensitivity and specificity under various conditions e.g. interference of the assay with bloody FNA and genomic DNA. The literature search revealed one study (Walsh and colleagues, 2012) that evaluated the analytic performance of Afirma GEC in a number of sub-studies. The investigators obtained prospective FNA samples aspirated in vivo from 43 patients from outpatient clinics, preoperatively, or immediately after surgical excision. The samples were placed in FNAProtect preservative solution and shipped chilled or frozen, then stored at -80^{o}C upon receipt. The RNA was extracted, and its yield examined for quantity and quality using positive (tissue lysate) and negative (water) as controls. Three different lots of controls were tested over several weeks of independent runs by 3 different operators to determine reliability of the test. Multiple lots of benign and malignant total RNA were manufactured and used as process controls to determine the analytic sensitivity of the test using different RNA input quantity and under different dilution of malignant FNA content. These studies indicated tolerance to variation in RNA input across a range of 5-25 ng. as well as dilution of malignant FNA material down to 20%. Analytic specificity of the test using malignant samples mixed with blood (up to 83%) and genomic DNA (up to 30%) showed minimal assay interference. However benign FNA samples mixed with relatively high proportions of blood had a potential for yielding false positive results. The investigators examined the stability of RNA in FNAs during collection and shipment and found that RNA content within FNAs preserved in FNAProtect was stable for up to 6 hours at room temperature with no change in RNA yield, and that the FNA storage and shipping temperatures had no significant effect on GEC scores. They also examined the reproducibility of the test and indicated that it was reproducible from extraction through GEC results, including variation across operators, runs, reagent lots, and laboratories. The investigators concluded that the analytical performance and reproducibility of the Afirma Gene Expression Classifier was successfully verified. The research was supported by Veracyte Corporation (the maker of Afirma GEC), and the authors of the study had financial ties to the corporation.

Clinical validity of Afirma GEC an ideal diagnostic test would have high sensitivity and specificity to correctly detect or exclude a condition. A molecular diagnostic test with high sensitivity offers a high negative predictive value (NPV) when the risk of malignancy is low and can "rule out'' malignancy. Conversely, a test with high specificity offers high positive predictive (PPV) value and can "rule in" malignancy. A preoperative diagnostic test would ideally have a high sensitivity in order not to miss a malignant nodule and have a high NPV to avoid surgery in patients with benign nodules. Predictive values do not only depend on the sensitivity and specificity of the test, but also on the prevalence of the disease; e.g. as the disease prevalence increases, the NPV decreases and vice versa. Afirma GEC test was validated in a. a double-blind prospective multicenter study (Alexander 2012 (Evidence table 1, reviewed earlier by MTAC). The study involved 265 nodules with indeterminate cytology that were selected for GEC analysis. Molecular results were compared to the gold standard of post-surgical histopathology. The malignancy rate was 32% and the Afirma sensitivity and specificity were 92% and 52% respectively with a NPV of 94-95% and PPV of 27-38% for Bethesda III/IV nodules. In the subgroup in patients with nodules suspicious for malignancy (SUSP) the NPV was only 85%, based on which, the authors concluded that GEC should not be used for cytology SUSP nodules. The study was conducted to validate the GEC accuracy by comparing it to surgical histopathology and did not compare its performance to repeat FNA or other immunochemical or molecular testing. A number of

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post-validation analyses were conducted by independent or industry supported investigators. In the initial validation study (Alexander 2012) the decision to resect the nodule was made independently of the GEC test results, while in the post-validation studies GEC was a factor influencing the decision whether to recommend a diagnostic surgical intervention. The published studies and analyses showed a wide variation in the NPVs and PPVs of Afirma GEC test results. The NPV and PPV of a test are neither absolute nor inherent in the test but depend on the pre-test probability of malignancy in the population studied, i.e. prevalence of malignancy in indeterminate nodules. This is made clear by Marti and colleagues (2014) who retrospectively analyzed all indeterminate thyroid nodules (ITNs) evaluated with GEC at two centers with widely different prevalence of malignancy in ITNs (Memorial Sloan Kettering Cancer Center [MSK] and Mount Sinai Beth Israel [MSBI]) (see table below).

The results of the validation study as well as post-validation studies are summarized in the following table.

Performance of GEC in the validation study and selected post-validation studies

Study	N FNA ITN undergoing GEC	Afirma results Suspicious	Benign	Inadequate RNA/ no result	Cancer prevalence in indeterminate FNA	NPV‡	PPV‡‡	Operative rate in GEC benign results
Alexander 2012 (multicenter Validation study)	265	62%	38%		32%	94-95%	27-38%	NA
Alexander, 2014 (5 centers)***	339	40%	55%	5%	--	99.4%	--	6.3%*
Harrell, 2014 (One practice)	58	62%	35%	3%	33-36%	88.3-89.6%	56%	25%**
McIver, 2014	72	61%	22%	17%	17%	94%	15.6%	25%
Marti, 2015 MSK center(tertiary) MSBI comprehensive health system)	 94 71	 74% 48%	 26% 52%	 -- --	 30-38% 10-19%	 86-92% 95-98%	 57.1% 14.3%	 8% 14%
Chaudhary, 2016†	158	54%	40%	6%		100%	38%	13%
Witt, 2016 (single-practice)	32	47%	44%	9%	21%	100%	--	0
Samulski, 2016 (single institution)	294	46%	49%	5%		81% for resected nodule, 98% for unrested benign GEC	39%	12%
Sacks, 2016 (single medical center)	140	55.7%	37.1%	7.1%	31.5%	92%††	33.3%	

All studies were performed in Institutional Enabled Centers, except for Harrell (2014) study where the cytology specimens were sent to Thyroid cytopathology partners (TCP).

* 1/11 (9.1%) was malignant (false negative)

** Of the 20 benign GEC patients 5 underwent surgery 2 of which (40%) were found to be malignant (False negative),

*** There were variation between the 5 study sites in the cytology distribution and Afirma GEC performance. GEC suspicious cases proved to be cancerous in 44% of cases (False positive in 56% of cases)

‡ The NPVs (the probability of cancer in GEC benign nodules) were all estimates and could not be directly assessed because not all patients had undergone surgery to determine surgical pathology or had long-term follow-up of the GEC benign nodules.

‡‡ The reported PPVs ranged between studies from 14-57% which limits the utility of the test as a rule-in test i.e. to predict the risk of malignancy.

† A comparison between pre- and post-GEC era showed no significant difference in surgical excision rates of FNA ITN. There were differences in the accuracy and predictive values of the GEC according to the cytomorphological features of the nodules. The authors concluded that the GEC test was found to reduce surgical excision of nodules with suspicious for follicular neoplasm (SFN), but not with FLUS / AUS or Hurthle cell neoplasm (HCN). They recommended repeating FNA rather than performing Afirma GEC test for FLUS/AUS, and be cautious when ordering GEC on HCN cases. 8 (13%) of the benign affirm underwent surgery and all were found benign

†† Estimated based on the prevalence. Cold not be calculated due o the low number of GEC-benign cases with surgical pathology

-- Not provided

Based on the results of the published studies, some investigators suggest that Afirma GEC may provide useful information in practice settings where the prevalence of malignancy in indeterminate thyroid nodules is 15-21%. At this range and using the sensitivity and specificity data from the multicenter validation study the NPV would be >95% and the PPV >25%. It is suggested that GEC may also provide some useful information with the prevalence of malignancy ranging from 12-25% but is not expected to be useful in altering management if the prevalence is outside this range (Marti 2015, Zhang 2016). The Afirma GEC performance was found to be suboptimal for Hurthle cell neoplasms (HCNs). Wu and colleagues (2016) examined the clinical factors influencing the performance of GEC testing and found that the test has a limited clinical validity for HCNs due to the high rate of false positive results (specificity 22.7-26.1% and PPV 29.2%). Other studies also showed inconsistent and low performance of GEC testing for HCN nodules. In the clinical validation study only 4 of 21 (19%) FNA samples from Hurthle

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adenomas were classified as benign with GEC.

Limitations in the published studies These include but are not limited to the following:

- All analyses were retrospective with potential bias and confounding.
- There were intra- and inter-observer differences within and between studies in the histological interpretations.
- Only data for patients with GEC testing were analyzed and with the exception of one study, the results were not compared to repeat FNA or other tests.
- The NPVs were all estimates as only a very limited number of GEC benign nodules underwent surgery, and the follow-up duration was too short to determine the true benign nature of the GEC benign nodules.
- The majority of the published studies were industry sponsored.
- The predictive values of a test vary with the prevalence of the disease in a population studied and may not be generalized to other groups. A better analysis would be the likelihood ratios which are not affected by prevalence.

Santhanam and colleagues' meta-analysis (2013, Evidence table 2) pooled the results of 7 prospective and retrospective studies to determine the sensitivity and specificity of the GEC test in classifying FNA indeterminate thyroid nodules and evaluate its clinical utility. The results of the meta-analysis are summarized in the following table:

Pooled results

Pooled values	Value (95% CI)	P value
Sensitivity	95.7% (92.2-97.9)	0.09
Specificity	30.5% (26.0-35.3)	<0.01
Positive likelihood ratio*	1.20 (0.99-1.44)	<0.01
Negative likelihood ratio**	0.2 (0.11-0.36)	0.56
Diagnostic odds ratio	7.86 (4.1-15.01)	0.42
Prevalence of malignancy	37.1%	
Positive predictive value	44.8 (40.4-49.4)	

*A good test for ruling-in a disease is the one with the largest positive likelihood ratio (LR) A positive LR of 1 means that the test does not provide any information on ruling in the disease, LR >1<5 indicates a small effect, and LR>10 indicates a large effect on increasing the probability of a disease is presence.

** The better test to rule-out a disease is the one with the smaller negative likelihood ratio. LR <0.1 indicates that the result has a large effect on decreasing the probability of the disease (rule out), LR 0.1-0.5 indicates moderate effect, and >0.5 indicates a small effect. The meta-analysis had valid methodology, but a meta-analysis is as good as the studies it includes. Due to the lack of RCTs and comparative prospective studies Santhanam and colleagues pooled the results of observational prospective and retrospective studies. There was significant heterogeneity between the studies as they were performed at different institutions and included a wide distribution of patients with different indeterminate cytology results (the test may perform better for one type of neoplasm/cancer versus the other). The meta-analysis had the advantage of calculating likelihood ratios which are not affected by prevalence the condition as the predictive values. However, likelihood ratios are calculated based on the sensitivity and specificity of the test, which may have not been accurate as the majority of GEC benign cases did not undergo surgery or were followed up for a sufficient duration to assess the actual accuracy of the test, and not all GEC suspicious cases underwent surgery. More recently in 2016, an international panel of pathologists and clinicians reclassified a clinically indolent malignant tumor (encapsulated follicular variant of papillary thyroid carcinoma [EFVPT]) as a benign neoplasm (noninvasive follicular thyroid neoplasm with papillary-like nuclear features [NIFTP]) (Niktforov 2016). This reclassification may affect the calculated performance of the current Afirma GEC as it has not been validated with these changes. In one study Samulski and colleagues (2016) reported that of 11 NIFTP cases in their cohort, only one was classified as benign with the GEC test.

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Clinical utility of Afirma GEC the clinical utility of Afirma GEC would be guiding the management decisions by clearly ruling out malignancy in FNA indeterminate nodules to avoid unnecessary diagnostic surgery. The published studies on the impact of Afirma GEC on the management of patients with FNS ITNs were retrospective in nature, performed in different sites with intra- and inter-rater variability, which are potential sources of selection and performance bias. In addition, the studies only focused on nodules that underwent Afirma GEC testing and did not investigate the effect of FNA results on overall thyroidectomy rates, or include a comparison group to examine the impact of a repeat FNA or other tests for nodules with indeterminate cytopathology. Santhanam and colleagues (2013, Evidence table 2) discussed in the previous section on clinical validity of Afirma GEC also evaluated its clinical utility of the test. The authors calculated that for patients with FNA indeterminate nodule, one thyroid surgery can be avoided for every two Afirma GEC tests, assuming that >90% of the patients with benign GEC are followed conservatively. They noted however, that according to the American Cancer Society, the 5-year survival of stage I and stage II follicular and papillary thyroid cancer is 100%. The morbidity and mortality rates in patients with FNA indeterminate thyroid nodules are reported to be more likely low, and thus the diagnosis of suspicious nodules with GEC testing may represent a lead-time bias with little change in overall survival.

Sacks and colleagues (2016 Evidence table 3) performed a retrospective analysis to evaluate the impact of Afirma GEC testing on cytopathology diagnosis, rate of surgery, and the rate of malignancy on all indeterminate nodules (ITNs) before and after the introduction of Afirma GEC testing at a high-volume thyroid center. The study was a retrospective analysis of patient data from one institution, with no direct comparison to a control group. However, it had the advantage of reporting on outcomes of repeat FNAs, comparing two cohorts' pre-and post-Afirma, and reporting on thyroidectomy rates among all cases irrespective of GEC testing. The calculated PPV for the test was 33.3%, and the estimated NPV was 92% (an accurate NPV could not be calculated due to small number of GEC benign cases with surgical pathology). There was a significant increase Bethesda III-IV diagnosis in the post Afirma cohort compared to the pre-Afirma cohort (13.4% vs. 10.7%, $p<0.005$), with a corresponding significant decrease in benign cytology (Bethesda II) post-Afirma (74.6% compared to 68.8% pre-Afirma, $p<0.001$), despite the use of the same guidelines, practice, reporting scheme, and personnel. In an attempt to explain the reason for this shift, the authors supposed that cytopathologists, especially those with less experience, may be less likely to classify nodules as Bethesda II knowing that the GEC testing will help stratify them. No significant changes were observed for Bethesda I, V, or VI, or in the rate of repeat FNA for ITNs. The author noted that while Afirma may reduce the rate of thyroidectomy for nodules with benign GEC results, the "suspicious label" may increase it. Only 33.3% of GEC suspicious cases were found to be malignant. The analysis shows that 35.2% of patients with ITNs who underwent a repeat FNA were classified as non-ITN and avoided Afirma testing. Overall, the results of the analysis indicate that the use of Afirma GEC testing was associated with an increase in the rate of FNA indeterminate diagnosis, and a decrease in the incidence of benign diagnosis. GEC testing did not reduce the overall rate of thyroidectomies which is its main goal. As indicated earlier the study had its disadvantages, which may limit generalization of the results.

Abeykoom and colleagues (2016), performed a similar respective analysis in a single endocrine clinic comparing the rate of surgeries pre-and post GEC testing for nodules with indeterminate cytopathology (N=61 [27 before and 34 after GEC implementation]). The results were however, inconsistent with Sack's 'findings. The analysis showed no significant difference before and after GEC implementation in the rate of ITNs, but there was a significant decrease in the recommendation for surgery for patients with ITNs from 81.5% pre-GEC implementation to 50% post GEC ($p=0.01$). The surgical pathology for those who underwent an operation was read as malignant in 20% and 85.7%. of patients before and after Afirma GEC respectively ($p<0.01$). The study was retrospective, small, included patients from a single center over two-time periods with different pathologists analyzing the specimens, which are potential sources of confounding and bias that may limit generalization of the results.

Duick and colleagues (2012, Evidence table 4, from an earlier MTAC review) performed a chart review for 21 endocrinology practices in 11 states. They analyzed data for 368 patients with 395 cytologically indeterminate thyroid nodules with Afirma GEC benign results. 7.6% of these patients underwent surgery and 94.4% were managed nonoperatively.

The study did not have a comparison group, but the authors compared the 7.6% surgical rate in nodules with benign GEC results to a 74% historical rate of diagnostic surgery ($P<0.001$). The main indications for surgery for those with GEC benign results were the rapid growth or larger size of the nodules, local pressure symptoms, or the presence of a second suspicious nodule or malignant nodule.

The study was retrospective, used a historical comparison, and investigated the decision-making of endocrinologists experienced in managing patients with thyroid nodules, which may differ from that made by primary care providers or other specialists. In addition, the authors of the study did not provide data on long-term

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follow-up of those who were managed by watchful waiting rather than surgery.

Sipos and colleagues (2016), retrospectively analyzed data recorded for 98 patients with a benign GEC over a mean duration of 36 ±3 months (range 0-44 months) treated at multiple centers. 17 of these 98 patients (17.3%) underwent surgery during this period. 88% of the surgeries were performed in the first 2 years after the benign GEC results with the rate leveling after the first year. The most common indications for surgery were the nodules rapid growth and large size. The authors concluded that the study shows that benign GEC test results are associated with low operative rates. The study had its limitations and the authors did not provide data on the pathology results of the resected nodules.

Articles: The updated literature search revealed a number of retrospective analyses performed after the Afirma GEC validation study, a meta-analysis that pooled the results of selected studies, and three retrospective studies on the clinical utility of the test. The study on the analytic validity, the two clinical validation studies as well as two retrospective studies on clinical utility were reviewed earlier by MTAC. The meta-analysis and the more recent studies on the clinical validly and clinical utility of Afirma GEC test were reviewed and their results summarized.

04/12/2022: MTAC Review
Thyroid Nodule Molecular Testing

Evidence Conclusion: Analytical validity: One study showed that Afirma GSC test has a strong analytic performance and is reproducible. Clinical validity: Low quality evidence suggests that: Afirma GSC test has a good diagnostic performance. Comparison to ThyroSeq v3 and ThyraMIR/ThyGeNEXT: the diagnostic performance cannot be ranked due to lack of head-to-head comparisons. Clinical utility: The evidence is insufficient (very low quality) for or against the use of Afirma GSC to reduce unnecessary surgery in patients with indeterminate thyroid nodules.

Articles: PubMed was searched through October 26, 2021. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Search terms included: (Afirma Genomic Sequencing Classifier OR Genomic Sequencing Classifier OR GSC OR Afirma OR Veracyte) AND (thyroid) through 10/21/21.
For Thyroseq v3, search terms included ThyroSeq v3Regarding ThyGeNEXT and ThyraMIR, search terms included Interpace or ThyGeNEXT or ThyraMIR. Afirma GSC: The search yielded several articles. After screening through abstracts and/or full text, 9 studies were retained and reviewed. The studies consisted of 1 analytical validity study, four clinical validity studies, and four clinical utility studies. Thyroseq v3: The search yielded several articles. Studied retained are critically appraised. ThyGeNEXT and ThyraMIR: The search yielded several articles. Studied retained are critically appraised. See Evidence tables.

The use of Thyroid Nodule Molecular Testing does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Intellectual Disability

BACKGROUND

Intellectual disability, also termed mental retardation or cognitive disability, affects approximately 1-3% of the general population and is defined as a significant impairment in cognitive and adaptive functions, with the age of onset before 18 years. It is a serious and lifelong condition that presents significant challenges to families and to public health. Determining the specific etiology of intellectual disability may help to provide answers related to prognosis, recurrence risk, and treatment. Intellectual disability can be caused by anything that damages or interferes with the growth or maturation of the brain; however, genetic (chromosomal) abnormalities are one of the main causes of intellectual disability (Galasso 2010, Sagoo 2009). Chromosomal abnormalities are deletions and duplications of genomic material and are commonly referred to as copy number variations. Conventional methods for detecting these abnormalities include karyotyping and florescent in situ hybridization (FISH). Karyotyping involves visualizing the chromosome for large gains or losses in chromosomal material and is generally the first step in cytogenetic analysis. Karyotyping can detect chromosomal abnormalities such as deletions, duplications, inversions, and translocations across the entire genome; however, it lacks the resolution necessary to detect abnormalities smaller than 3-5 megabases (Mb; 3-5 million base pairs). FISH uses florescent-labeled chromosome-specific probes to detect chromosomal abnormalities. FISH can detect submicroscopic abnormalities and is often used in situations where the karyotype is normal, but there is a high clinical suspicion of a deletion syndrome. However, FISH is a targeted method and requires prior knowledge of the chromosome region(s) of interest to request the appropriate FISH test. Additionally, FISH can only screen a limited number of genomic regions at a time (Breman 2009, Fruhman 2010, Galasso 2010, Gropman 2010). Array comparative genomic hybridization (aCGH) is a more recent technology used to identify copy number variations by comparing

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patient DNA with reference DNA. It is currently used as an adjunct to conventional methods. There are two types of aCGH: targeted and whole-genome. Targeted arrays are designed to interrogate areas of the genome with known clinically significant abnormalities. Whole genome arrays provide high resolution coverage of the entire genome. This can lead to the discovery of new copy number variations. Compared to conventional methods, aCGH has a higher resolution and is able to simultaneously detect copy number variations in multiple regions of the genome. Additionally, unlike FISH, knowledge of the chromosome region(s) of interest does not need to be determined in advance because a single array assay detects all genomic variants represented on the array. Array CGH is not without limitations. It cannot detect totally balanced translocations or inversions; it performs suboptimally for polyploidy; and has not been optimized for prenatal diagnosis of point mutations. Because aCGH cannot identify the exact location of a duplicated chromosome, further testing with karyotype or FISH may be necessary. Another limitation is the potential to identify novel copy number variants with unknown clinical significance (Fruhman 2010, Moeschler 2008). Array CGH is a laboratory-developed test and is commercially available from several different laboratories. Laboratory-developed tests are licensed under the Clinical Laboratory Improvement Amendments (CLIA) and do not require clearance from the FDA.

The use of Gene Expression Classifier (Afirma®) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

4/18/2011: MTAC REVIEW

Array Comparative Genomic Hybridization (aCGH) for the Genetic Evaluation of Patients with Intellectual Disability

Evidence Conclusion: Analytic validity The BCBS review identified several studies that evaluated the sensitivity of aCGH. The sensitivity of aCGH testing compared to conventional methods (karyotype and/or FISH) ranged from 73% to 100%. As false-positive rates were inconsistently reported, specificity could not be determined (BCBS 2009). Clinical validity

Articles: No studies were identified that evaluated the impact of conventional methods or aCGH on patient outcomes other than diagnostic yield. Results from the BCBS review suggest that diagnostic yield in patients with intellectual disability ranged from 5 to 16.7%, which represents a significant improvement compared to conventional methods. The number needed to test by aCGH to detect one clinically relevant abnormality ranged from 25 to 6 depending on the diagnostic yield. Limitations of these studies include: different aCGH resolution, patient selection criteria ranged from none too stringent criteria, and three different types of arrays were used (targeted, whole-genome, and those that combined targeted and whole-genome arrays) (BCBS 2009).

Diagnostic yield[1] of aCGH, karyotype, and FISH

	aCGH	FISH	karyotype
Diagnostic yield	4-7% (In those negative by karyotype and FISH)	5-6% (In those negative by karyotype)	3-5%

[1]Estimates from Stankiewicz 2007.

Clinical utility The BCBS review included two small studies with a high risk of bias and found that there was insufficient evidence to determine the clinical utility of aCGH testing (BCBS 2009). Conclusion: Analytic validity: There is fair evidence that aCGH testing had good sensitivity compared to conventional methods; however, there is insufficient evidence to determine the specificity or reproducibility of this test. Clinical validity: There is fair evidence that aCGH increases diagnostic yield over conventional methods; however, this is an intermediate outcome. Clinical utility: There is insufficient evidence that patients managed with the genetic test had better outcomes than patients managed without the genetic test.

In 2009, Blue Cross and Blue Shield (BCBS) evaluated the use of aCGH for the genetic evaluation of patients with developmental delay/ mental retardation. Studies were selected for review if they were published after the 2009 review and did not support the BCBS recommendations. No studies were identified that would change the BCBS recommendations. The following review was critically appraised: Blue Cross and Blue Shield Association.

Special report: aCGH for the genetic evaluation of patients with developmental delay/mental retardation or autism spectrum disorder. Assessment Program. Volume 23, No. 10. April 2009.

The use of Array Comparative Genomic Hybridization (aCGH) for the genetic evaluation of patients with intellectual disability does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

HLA Testing for Celiac Disease

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BACKGROUND

Celiac disease is a chronic, autoimmune disorder that affects approximately 1% of children and adults in the United States. In individuals with celiac disease, the ingestion of gluten proteins found in wheat, rye, and barley lead to an autoimmune reaction that causes small intestine mucosal injury. Damages in the small intestine can cause gastrointestinal symptoms and interfere with the absorption of nutrients from food. This may lead to malnutrition-related problems such as anemia, vitamin deficiencies, osteoporosis, and neurological disorders. A gluten-free diet typically resolves symptoms and can prevent long-term consequences (Tack 2010). There are a variety of tests available to diagnose celiac disease. The gold-standard for diagnosing celiac disease is a small intestine biopsy. However, this test is not a perfect gold-standard as false positive and false-negative results may occur due to interobserver variability, patchy mucosal damage, low-grade histological abnormalities, and technical limitations. Additionally, histological features are not unique to celiac disease. Serum antibody tests are used as an initial screening tool to detect and support the presence of celiac disease and to select which patients should undergo a biopsy. Two of the most sensitive and specific serological tests for diagnosing celiac disease are tests that assess the presence of IgA autoantibodies against the endomysium of connective tissue (EMA) (sensitivity 62-81%, specificity 80-99%) and against tissue transglutaminase (tTGA) (sensitivity 81-88%, specificity 84-99%). While these tests are accurate, they are not without limitations. For example, the EMA test correlates with the degree of mucosal damage. As such, the sensitivity of this test is lower in patients with milder cases (higher chance of false negative results). Additionally, false negative results may occur in patients with an IgA deficiency and in patients who are already on a gluten-free diet. In patients with an IgA deficiency, serum IgA testing can be replaced by using IgG assays, which are less sensitive than IgA assays. Another test that can be used to rule out the diagnosis of celiac disease is human leukocyte antigen (HLA) genotyping. It has been reported that approximately 90-95% of patients with celiac disease are carriers of the HLA-DQ2 heterodimer and most of the remaining patients carry the HLA-DQ8 heterodimer. Since virtually all patients with celiac disease carry one of these heterodimers, celiac disease is highly unlikely when both are absent. It has been proposed that using HLA genotyping as an initial screening tool may avoid future concerns about the condition and eliminate further diagnostic testing. However, HLA typing is not a perfect solution since around 25-40% of the general population carries either HLA-DQ2 or DQ8, of which the majority never develop the disease. Other situations where HLA genotyping may be useful is when the diagnosis of celiac disease is unclear based on serological and/or histological findings. Additionally, HLA genotyping can be performed in patients who are already on a gluten free diet (Tack 2010, Hadithi 2010).

4/18/2011: MTAC REVIEW

HLA Testing for Celiac Disease

Evidence Conclusion: Analytic validity There are a variety of methods used for HLA genotyping. Each of these assays has its advantages and limitations (Monsuur 2008, Lavant 2009). Clinical validity A recent prospective cohort study evaluated the accuracy of serologic tests and HLA-DQ genotyping used alone and in combination for diagnosing celiac disease compared to small intestine biopsy. Results from this study suggest that both tTGA and EMA are sensitive and specific tests for diagnosing celiac disease. HLA-DQ testing was also highly sensitive but was not as specific as serologic testing. The addition of HLA-DQ genotyping to serum antibody tests did not increase test performance compared to serologic testing alone. Results should be interpreted with caution as only 16 patients were diagnosed with celiac disease (Hadithi 2007). Sensitivity and specificity of serologic testing and HLA-DQ typing for diagnosing celiac disease

	Sensitivity (95% CI)	Specificity (95% CI)
HLA-DQ testing		
HLA-DQ2 or DQ8	100 (79-100)	57 (52-62)
Serologic testing using IgA		
tTGA	81 (54-95.9)	99.1 (97.7-99.7)
EMA	81 (54-95.9)	99.1 (97.7-99.7)
tTGA & EMA	81 (54-95.9)	99.3 (98-99.9)
Both serologic testing & HLA-DQ testing		
tTGA & HLA-DQ	81 (54-95.9)	99.3 (98-99.3)
EMA & HLA-DQ	81 (54-95.9)	99.1(97.7-99.8)
tTGA, EMA, & HLA-DQ	100 (79-100)	99.3 (98-99.9)

Abbreviations: EMA= antiendomysium antibody; tTGA= antitransglutaminase antibody.

Another observational study investigated whether HLA genotyping would be useful to identify first-degree relatives of patients with celiac disease who do not need further screening for celiac disease. Fifty-four families with at least two siblings with celiac disease were selected to participate in the study. In total, 245 (52.5%) first-degree relatives agreed to participate. The diagnosis of celiac disease was based on duodenal biopsy and medical records. Of all of the first-degree relatives, 17.6% (N=43) did not carry any of the celiac disease risk alleles. Of these relatives, only one was diagnosed with celiac disease (Karinen 2010). Clinical utility

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Because of its low specificity HLA genotyping may not be an ideal initial screening test for diagnosing celiac disease. However, HLA genotyping may be useful in certain situations, such as when the diagnosis of celiac disease is unclear based on serologic and histologic findings and when patients are already on a gluten free diet, to rule out celiac disease. Additionally, as negative serologic or histologic test results do not exclude the development of celiac disease later in life, the use of HLA genotyping in patients who are at increased risk for celiac disease may prevent unnecessary serologic and histologic testing. Conclusion: Analytic validity: There are a variety of methods used for HLA genotyping. Each of these assays has its advantages and limitations. Clinical validity: There is fair evidence that HLA genotyping may be a useful adjunct in the diagnosis of celiac disease as it has a high negative predictive value. Clinical utility: No studies were identified that addressed the clinical utility of HLA genotyping for celiac disease; however, early identification and treatment of the disease can prevent short- and long-term complications.

Articles: Articles were selected for review if they included at least 25 subjects and assessed the accuracy of HLA genotyping compared to the small intestine biopsy. A prospective cohort study was selected for review. The following study was critically appraised: Hadithi M, von Blomberg ME, Crusius BA, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Ann Intern Med 2007;* 147:294-302. See Evidence Table

The use of HLA testing for celiac disease does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Micro Array for Evaluation of Intellectual Disability

BACKGROUND

Intellectual disability, also termed mental retardation or cognitive disability, affects approximately 1-3% of the general population and is defined as a significant impairment in cognitive and adaptive functions, with the age of onset before 18 years. It is a serious and lifelong condition that presents significant challenges to families and to public health. Determining the specific etiology of intellectual disability may help to provide answers related to prognosis, recurrence risk, and treatment.

Intellectual disability can be caused by anything that damages or interferes with the growth or maturation of the brain; however, genetic (chromosomal) abnormalities are one of the main causes of intellectual disability (Galasso 2010, Sagoo 2009).

Chromosomal abnormalities are deletions and duplications of genomic material and are commonly referred to as copy number variations. Conventional methods for detecting these abnormalities include karyotyping and florescent in situ hybridization (FISH). Karyotyping involves visualizing the chromosome for large gains or losses in chromosomal material and is generally the first step in cytogenetic analysis. Karyotyping can detect chromosomal abnormalities such as deletions, duplications, inversions, and translocations across the entire genome; however, it lacks the resolution necessary to detect abnormalities smaller than 3-5 megabases (Mb; 3-5 million base pairs).

FISH uses florescent-labeled chromosome-specific probes to detect chromosomal abnormalities. FISH can detect submicroscopic abnormalities and is often used in situations where the karyotype is normal, but there is a high clinical suspicion of a deletion syndrome. However, FISH is a targeted method and requires prior knowledge of the chromosome region(s) of interest to request the appropriate FISH test. Additionally, FISH can only screen a limited number of genomic regions at a time (Breman 2009, Fruhman 2010, Galasso 2010, Gropman 2010).

Array comparative genomic hybridization (aCGH) is a more recent technology used to identify copy number variations by comparing patient DNA with reference DNA. It is currently used as an adjunct to conventional methods. There are two types of aCGH: targeted and whole-genome. Targeted arrays are designed to interrogate areas of the genome with known clinically significant abnormalities. Whole genome arrays provide high resolution coverage of the entire genome. This can lead to the discovery of new copy number variations. Compared to conventional methods, aCGH has a higher resolution and is able to simultaneously detect copy number variations in multiple regions of the genome. Additionally, unlike FISH, knowledge of the chromosome region(s) of interest does not need to be determined in advance because a single array assay detects all genomic variants represented on the array. Array CGH is not without limitations. It cannot detect totally balanced translocations or inversions; it performs suboptimally for polyploidy; and has not been optimized for prenatal diagnosis of point mutations.

Because aCGH cannot identify the exact location of a duplicated chromosome, further testing with karyotype or FISH may be necessary. Another limitation is the potential to identify novel copy number variants with unknown clinical significance (Fruhman 2010, Moeschler 2008).

Array CGH is a laboratory-developed test and is commercially available from several different laboratories.

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Laboratory-developed tests are licensed under the Clinical Laboratory Improvement Amendments (CLIA) and do not require clearance from the FDA.

Date: 07/09/2018 MTAC REVIEW

Chromosomal microarray for Intellectual Disability (ID)/ Developmental delay (DD)

BACKGROUND

Intellectual disability is a disorder marked by deficits in intellectual and adaptive functioning and starts before 18 years of age. Its management requires early diagnosis and extensive supports. Intellectual disability is caused by any conditions disrupting brain development. Of these conditions, genetic abnormalities are the most common known etiologies (Rauch et al., 2012) with Down syndrome being the leading cause. Conventional cytogenetics (karyotype analysis and fluorescence in situ hybridization (FISH)) can identify the cause but detect less than 10% of chromosomal abnormalities in patients with intellectual disability (ID) or developmental delay (DD) (Shaffer, Beaudet, et al., 2007; Shaffer, Bejjani, et al., 2007). Chromosomal microarray analysis (CMA) has become the primary test for most patients with intellectual disability (Miller et al., 2010). CMA includes array-based comparative genomic hybridization (aCGH) or single nucleotide polymorphism (SNP) microarray analysis.

Array-based comparative genomic hybridization (aCGH), also known as oligonucleotide array comparative genomic hybridization utilizes both patient and control genomes. These DNAs are marked with fluorescent dyes and applied to the microarray. This step is followed by hybridization. Hybridization occurs when patient and control DNAs compete to attach to the microarray which is comprised of thousands of DNA segments (bacterial artificial chromosome clones of > 10 kilobases or oligonucleotides of 50–70 base pairs). Fluorescent signals are assessed by a scanner and a computer analyzes the data and generates a plot. This results in the identification of copy number changes (Theisen et al., 2008(Shaffer et al., 2008)). It is believed that the aCGH concurrently detects copy number variants (CNVs) (deletions, duplications), and/or amplifications across the genome. However, the array-based comparative genomic hybridization cannot detect low-level mosaicism or balanced chromosomal rearrangements (Brady & Vermeesch, 2012). The results of the CMA are interpreted as benign with no impact on phenotype, or pathogenic/clinical significant, or uncertain clinical significance. In the latter category, samples from parents are required for assessment of the clinical significance (Miller et al., 2010; Paciorkowski & Fang, 2009). If the CMA does not detect a cause, whole exome sequencing (WES) may be performed. Single nucleotide polymorphism (SNP) arrays is a variation of DNA sequence that occurs when there is a discrepancy between a single nucleotide and a reference sequence in the same person. Single nucleotide polymorphism is used as the probes. Only the patient sample is hybridized onto the array(Das & Tan, 2013). SNP can detect copy number changes, uniparental disomy, consanguinity, and balanced translocations (Conlin et al., 2010; Schaaf, Wiszniewska, & Beaudet, 2011; Wiszniewska et al., 2014). No FDA regulatory information was found on FDA website on March 12, 2018. However, genetic tests are controlled under the Clinical Laboratory Improvement Amendments (CLIA). The technology is being assessed for the first time on Medical Technology Assessment Committee (MTAC).

Evidence Conclusion:

Conclusion:

- **Analytic validity:** Four studies were reviewed and showed high sensitivity and specificity with high concordance in comparison to FISH or karyotyping. This suggests that chromosomal microarray can accurately detect copy number variants in children and adolescents with developmental delay or intellectual disability. The studies were retrospective in design or case series resulting in low evidence.
- **Clinical validity:** Nine studies (please refer to “other studies table” and table 2) in addition to those included in Milliman review (evidence table 1) were evaluated. In children and adolescents with unexplained developmental delay or intellectual disability, chromosomal microarray (aCGH) diagnosed genomic alterations that were not detected by conventional cytogenetic tests including karyotype or FISH. This suggests that the detection rate of chromosomal microarray is higher than conventional cytogenetic tests. However, the studies reviewed were case series or retrospective chart review resulting in low evidence.
- **Clinical utility:** Two studies (please refer to “other studies table” and table 2) in addition to those included in Milliman review (evidence table 1) were evaluated. The clinical utility revolved around referrals to specialists, recommendation for screening of other anomalies, provision of recurrent risk for affected subsequent pregnancies, and avoidance of unnecessary testing. However, the studies were surveys and retrospective review with small sample size resulting in low evidence.
- Milliman Care guidelines indicated that there is a net benefit in evaluating children and adolescents with intellectual disability with chromosomal microarray analysis (CMA). The use of CMA to detect copy number variants affects medical management and this includes referrals to specialists, treatment intervention for special findings, reduction of unnecessary procedures, and screening for associated anomalies. However, the evidence is of low certainty.

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The use of Chromosomal microarray for Intellectual Disability (ID)/ Developmental delay (DD) meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/18/2011: MTAC REVIEW

Array Comparative Genomic Hybridization (aCGH)

Evidence Conclusion: Analytic validity - The BCBS review identified several studies that evaluated the sensitivity of aCGH. The sensitivity of aCGH testing compared to conventional methods (karyotype and/or FISH) ranged from 73% to 100%. As false-positive rates were inconsistently reported, specificity could not be determined (BCBS 2009). Clinical validity - No studies were identified that evaluated the impact of conventional methods or aCGH on patient outcomes other than diagnostic yield. Results from the BCBS review suggest that diagnostic yield in patients with intellectual disability ranged from 5 to 16.7%, which represents a significant improvement compared to conventional methods. The number needed to test by aCGH to detect one clinically relevant abnormality ranged from 25 to 6 depending on the diagnostic yield. Limitations of these studies include: different aCGH resolution, patient selection criteria ranged from none to stringent criteria, and three different types of arrays were used (targeted, whole-genome, and those that combined targeted and whole-genome arrays) (BCBS 2009).

Diagnostic yield[1] of aCGH, karyotype, and FISH

	aCGH	FISH	karyotype
Diagnostic yield	4-7% (In those negative by karyotype and FISH)	5-6% (In those negative by karyotype)	3-5%

[1]Estimates from Stankiewicz 2007.

Clinical utility- The BCBS review included two small studies with a high risk of bias and found that there was insufficient evidence to determine the clinical utility of aCGH testing (BCBS 2009).

Conclusion:

1. Analytic validity: There is fair evidence that aCGH testing had good sensitivity compared to conventional methods; however, there is insufficient evidence to determine the specificity or reproducibility of this test.

2. Clinical validity: There is fair evidence that aCGH increases diagnostic yield over conventional methods; however, this is an intermediate outcome.

3. Clinical utility: There is insufficient evidence that patients managed with the genetic test had better outcomes than patients managed without the genetic test.

Articles: In 2009, Blue Cross and Blue Shield (BCBS) evaluated the use of aCGH for the genetic evaluation of patients with developmental delay/ mental retardation. Studies were selected for review if they were published after the 2009 review and did not support the BCBS recommendations. No studies were identified that would change the BCBS recommendations. The following review was critically appraised: Blue Cross and Blue Shield Association.

Special report: aCGH for the genetic evaluation of patients with developmental delay/mental retardation or autism spectrum disorder. Assessment Program. Volume 23, No. 10. April 2009.

The use of Array Comparative Genomic Hybridization (aCGH) for the genetic evaluation of patients with intellectual disabilities does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Risk Prognosticator Test

BREVAGen

BACKGROUND

According to the American Cancer Society, breast cancer is the second leading cause of death in women in the United States after lung cancer. Current methods of assessing breast cancer risk include the Breast Cancer Risk Assessment Tool (BCRAT) otherwise known as the Gail model. This model incorporates individual risk factors such as basic demographic information, reproductive history and medical history. Recent genome wide association studies have identified several single nucleotide polymorphisms (SNPs) associated with an increased risk of breast cancer leading to an additional dimension and understanding of risk (Easton, Pooley et al. 2007; Stacey, Manolescu et al. 2007; Stacey, Manolescu et al. 2008). The BREVAGen™ (Phenogen Sciences, Inc., Charolette, NC) is a risk stratification test for sporadic breast cancer. Intended for use as an

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adjunct to the Gail model, the test consists of two parts, the first, a series of questions to determine clinical risk and the second, a buccal swab to analyze specific genetic markers. The latter part of the test, includes a panel of seven SNPs associated with breast cancer risk and does not include either of the BRCA mutations. Ultimately, a patient's risk is calculated by multiplying the product of the individual SNP risks by the Gail model risk. According to the BREVAGen™ website, the test is only suitable for women of European descent aged 35 years or older. No test combining the results of SNP analysis with clinical factors to predict breast cancer risk has been approved or cleared by the U.S. Food and Drug Administration (FDA). BREVAGen™ is offered as a laboratory developed tests and only requires oversight under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The development and use of this laboratory developed test is restricted to laboratories certified as high complexity under CLIA. Under the current regulatory program, CLIA requires that laboratories demonstrate quality systems which includes validation and proficiency testing.

12/16/2013: MTAC REVIEW
BREVAGen
Evidence Conclusion:
Conclusion: There is no evidence to determine the analytic validity of the BREVAGen™. There is some evidence to suggest that the addition of the BREVAGen™ panel is superior in determining breast cancer risk compared to Gail score alone. There is no evidence to determine the clinical utility of the BREVAGen™.
Articles: A search of PubMed was completed for the period through November 2013 for studies on the accuracy of BREVAGen™ for detecting the absence or presence of certain common genetic variations associated with an increased risk for developing breast cancer. The search strategy used the terms BREVAGen, Breast Cancer Risk Tool, Gail Model, genetic risk, single nucleotide polymorphism, breast cancer, and sporadic with variations. To identify ongoing clinical trials, a search of the National Institute of Health Clinical Trials website was also conducted using the same methodology. Articles were limited to those published in the English language with human subject enrollment. The search was supplemented by an examination of article reference lists in addition to the PubMed related articles function. The literature search for BREVAGen™ revealed one publication that clinically validates the Breast Cancer Risk Model in combination with the genetic and clinical information. The following study was selected for review: Mealiffe ME, Stokowski RP, Rhees BK, et al. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. *Journal of the National Cancer Institute*. 2010;102(21):1618-1627. See Evidence Table.

The use of BREVAGen does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Fibroblast Growth Factor Receptor 3 (FGFR3) for Urothelial Carcinoma
BACKGROUND
It is estimated that approximately 70,530 new cases of bladder cancer will be diagnosed in the United States in 2010, and 14,680 will die of the disease (Jemal 2010). The most commonly occurring form of bladder cancer in the United States is urothelial carcinoma (also known as transitional cell carcinoma). The clinical spectrum of urothelial carcinoma can be divided into 3 categories: non-muscle-invasive, muscle-invasive, and metastatic disease. This review will focus on non-muscle-invasive urothelial cancer (NMIUC), which makes up approximately 75-80% of urothelial carcinoma. NMIUC includes stage Ta (noninvasive papillary carcinoma), Tis (carcinoma in situ), and T1 (tumor invades subepithelial connective tissue) tumors. The standard treatment for stage Ta, Tis, and T1 tumors is transurethral resection of bladder tumor (TURBT). Depending on prognosis adjuvant intravesical chemotherapy or immunotherapy may also be considered. However, despite treatment a significant number of patients will develop recurrence within 1 to 2 years of the initial treatment. Because of the high risk of recurrence careful surveillance is required for patients with NMIUC (Chou 2010, Cheng 2011, NCCN 2011, Pollard 2010). Assessing the risk of progression and recurrence is important for planning therapy. The risk for tumor progression and recurrence is estimated using factors such as histological grade, stage, depth of invasion, and extent of disease; however, the ability of these factors to predict clinical outcome is limited (Burger 2008, Cheng 2011, NCCN 2011). Recently, it has been suggested that molecular biomarkers such as fibroblast growth factor receptor 3 (FGFR3) may be useful for predicting clinical outcome and planning therapy. FGFR3 regulates cell growth, differentiation, and angiogenesis. More than 70% of low-grade noninvasive papillary urothelial carcinomas harbor FGRF3 mutations. Studies suggest that urothelial carcinomas that harbor FGFR3 mutations may be associated with improved prognosis (Cheng 2011). The CertNDx molecular grading assay (Predictive Biosciences, Inc.) was designed as a tool to be used in conjunction with clinical and histological parameters to aid in the clinical management of NMIUC. This test uses two biomarkers to determine molecular grade. The first biomarker is FGFR3 and the second is Ki-67, which is a marker of cell proliferation (Cheng 2011). Patients with molecular grade 1 (mG1) have FGFR3 mutations and low Ki-67 levels. Patients with molecular grade 2 (mG2) have FGFR3 mutations with high Ki-67 levels or wild-type FGFR3 and low Ki-67 levels. Patients with molecular grade 3 (mG3)

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are FGFR3 wild-type and have high Ki-67 levels. Patients with molecular grade 1 have favorable prognosis, patients with molecular grade 2 have intermediate prognosis, and patients with molecular grade 3 have poor prognosis.

10/17/2011: MTAC REVIEW

Fibroblast Growth Factor Receptor 3 (FGFR3) for Urothelial Carcinoma

Evidence Conclusion: Analytic validity- No studies were identified that addressed the analytic validity of the CertNDx molecular grading assay. Clinical validity - A recent prospective observational study evaluated the prognostic value of both WHO 1973 and 2004 grading systems, markers CK20, FGFR3, and Ki-67, and molecular grade (combination of FGFR3 and Ki-67) in 221 patients with urothelial carcinoma. In univariate analysis, WHO grade 1973, WHO grade 2004, pathological stage, FGFR3, Ki-67 status, and molecular grade were significantly associated with progression in stage; however, in a multivariate model, only WHO grade 1973 and 2004 remained significantly associated with progression in stage. None of the variables measured were significantly associated with recurrence-free survival (Burger 2008). Another study that included 255 patients with primary urothelial carcinoma also found that the combination of FGFR3 and Ki-67 status was not an independent predictor of recurrence-free or disease-specific survival (van Oers 2007). However, an observational study that included 286 patients with urothelial carcinoma found that in a multivariate analysis, the combination of FGFR3 and Ki-67 status predicted progression, recurrence rate, and disease-specific survival (van Rhijn 2003). Clinical utility -
No studies were identified that addressed the clinical utility of the CertNDx molecular grading assay.
Conclusion: Analytic validity: No studies were identified that addressed the analytic validity of the CertNDx molecular grading assay. Clinical validity: Results from observational studies regarding the prognostic value of molecular grade (FGFR3/Ki-67) are mixed. Clinical utility: No studies were identified that addressed the clinical utility of the CertNDx molecular grading assay.
Articles: No studies were identified that addressed the analytic validity or clinical utility of the CertNDx molecular grading assay. Several studies were identified that evaluated the clinical validity of the CertNDx molecular grading assay. The most recent study was selected for review. The following study was critically appraised: Burger M, van der Aa MN, van Oers JM, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. *Eur Urol.* 2008;54:835-843. See Evidence Table.

The use of FGFR3 for urothelial carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

MammaPrint Test

BACKGROUND

Breast cancer affects almost 10% of women in western countries and is a major cause of morbidity and mortality. Most patients with lymph node negative disease may be successfully treated with surgery and local irradiation. Those with more aggressive disease may benefit from adjuvant chemotherapy and hormone therapy which could significantly improve their overall and disease-free survival. It is generally accepted that breast cancer patients with the poorer prognosis would gain the most benefits from systemic adjuvant therapy. The use of this adjuvant therapy is thus one of the most critical treatment decisions during the clinical management of breast cancer patients. Currently those with aggressive breast cancer are identified according to a combination of criteria including age, clinical stage and size of the tumor, histological type and grade of cancer, axillary node status, and hormone-receptor status. The ability of these criteria to predict outcome and disease progression is imperfect. Within a given patient population at a specific predicted risk of recurrence, there are some patients whose actual clinical outcome does not match that predicted by the indicators. As a result, some of those who need adjuvant therapy do not receive it, while others may receive unnecessary toxic therapy (Kallioniemi 2002, DeVigier 2002). To overcome these issues, scientists are attempting to identify more accurate prognostic indicators. Microarray technology is revolutionizing researchers' understanding of cancer biology through the simultaneous study of the expression of tens of thousands of genes. Molecular profiling is the classification of tissue or other specimens for diagnostic, prognostic, and predictive purposes based on multiple gene expression. The potential value of gene expression profiling in assessing the risk of post-surgical breast cancer recurrence has been extensively investigated over the last few years. This has led to important insights in the molecular heterogeneity of cancers by revealing biologically and clinically relevant subtypes of tumors previously indistinguishable by the conventional approaches (Bertucci 2005). Due to the biological heterogeneity of breast cancers, women with the same stage of the disease may vary widely in their response to treatment and prognosis. Several gene expression-based predictors for breast cancer have been developed but have not been used in routine clinical practice. According to researchers, this is mainly due to the limited validation and the limited clinical description of the molecular subtypes. Validation is a major challenge for microarray studies especially those with clinical implications as it

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requires a large sample size and because the results are influenced by the patient selection and by choice of the methods used to analyze gene expression data (Calza 2006, Hu 2006, Ioannidis 2007). The Amsterdam 70-gene profile (MammaPrint ®) was first developed using supervised gene expression profiling analysis of frozen tumor samples from two distinct patient populations. All were <55 years of age and had lymph node negative disease. 44% had distant metastases within 5 years of completing treatment and 56% did not. By comparing the gene expression profile of patients with or without metastases, a signature 70-gene set that correlated with the outcome was identified and internally validated with the same group (van't Veer 2002), and externally validated in two retrospective groups (Van De Vijver 2002 and Buyse 2006, see evidence tables). MammaPrint ® from Agendia is a qualitative in vitro diagnostic test service performed in a single laboratory using the gene expression profile of breast cancer tissue samples to assess a patient's risk for distant metastases. The MammaPrint assay uses a panel of the Amsterdam 70-gene profile described above. It is a microarray-based gene expression analysis of RNA extracted from breast tumor tissue. The MammaPrint ® analysis is designed to determine the activity of specific genes in a tissue sample compared to a reference standard. Its index ranges from -1.0 to +1.0. Tumor samples with an index above the threshold of +0.4 are classified as low risk, and those with an index equal to or less than the threshold is classified as high risk. The test requires fresh frozen samples which are shipped to the Agendia reference laboratory in the Netherlands. It is performed for breast cancer patients <61 years old, with Stage I invasive breast cancer or Stage II node negative invasive breast cancer, with tumor size <5 cm. It is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors. It is not intended for diagnosis, or for predicting or detecting response to therapy, or to help select the optimal therapy for patients (FDA).

08/06/2007: MTAC REVIEW
MammaPrint Test

Evidence Conclusion: The identification and validation of gene expression panels to improve risk prediction or treatment outcomes is a multistep process that starts by 1. Identifying the candidate genes (analytic validity), followed by 2. Evaluating the genetic panel associations with risk prediction or treatment outcomes in preliminary performance studies in relevant population (clinical validity), and 3. Determining whether the use of the multigenetic assay would direct the management of patients and improve outcomes (clinical utility). The most reliable method for validation is to derive a prognostic/predictive gene set from a training set and then apply it to a completely independent set, the test set, (Simon 2003, Ionnidis 2006, and Hu 2006). The MammaPrint test was developed based on research performed in the Netherlands Cancer Institute, The training set was derived from a study by van't Veer and colleagues that included 98 women < 55 years of age at diagnosis, with primary breast cancer (34 developed distant metastases within 5 years, 44 were disease free after at least 5 years). All patients were lymph node negative. 5 µg total RNA was isolated from frozen tumor material for each patient. The authors used inkjet-synthesized oligonucleotide microarrays that included 25,000 genes. Following several techniques 5000 genes were selected from the microarray, and then optimized to 70 genes with which a prognosis profile was established. The authors conducted a cross validation and concluded that a classification system based on these 70 genes outperformed all clinical variables in predicting the likelihood of distant metastases within five years.
They noted however, that a selection of the patients based on the outcome (distant metastases or disease free in 5 years) was a limitation to the study. The same research team followed the initial study with a validation study (Van De Vijver, 2002) that included 295 women with either lymph node negative or lymph node positive breast cancer. The authors calculated the correlation coefficient of the level of expression of the 70- predictor genes identified in their initial study. They then classified the women with a correlation coefficient > 0.4 as having a good prognosis gene expression signature, and all the others as having a poor prognosis gene expression signature. In this validation set however the authors included 61 patients from the original training group used to derive the RNA expression signature, which could overestimate the relative risk and inflate the discriminating power of the test.
The validation study included women < 55 years of age, with small tumors and at stage I or II of the disease which may not represent the entire spectrum of patients with breast cancer. Adjuvant hormone therapy or chemotherapy or both were given to most of the patients with lymph node positive disease. The Translational Research Network of the Breast International group (TRANSBIG) also conducted an independent validation study of the prognostic signatures in a retrospective series of 302 untreated patients in five European countries. The study included only women node negative early stage breast cancer who had not received systemic adjuvant therapy, and thus may not represent the all patients with breast cancer. Its overall results showed that the 70-gene signature provided prognostic information on time to distant metastases and overall survival independent of the other clinical predictors.
In conclusion, the selection of the 70- predictor genes were based on analyses of tumors from patients < 55 years of age with lymph node negative cancer who do not represent all women with breast cancer. The test proved to perform well as an independent prediction tool among the selected women studied. This, however, does not necessarily indicate that it would predict treatment response. To date there are no published studies that show if modification of adjuvant therapy based on this test would improve disease free or overall survival. A large

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randomized controlled trial (Microarray for Node negative Disease may Avoid Chemotherapy [MINDACT]) that will evaluate the clinical utility of MammaPrint is underway. The trial will directly compare the use of prognostic information provided by the standard clinicopathological criteria vs. the MammaPrint test to decide whether to offer adjuvant chemotherapy to node-negative breast cancer patients. The MINDACT plans to prospectively include 6000 women and follow-them up for a long duration in order to determine 5-year disease free-survival rate.

Articles: The literature search revealed multiple articles on molecular and gene-expression profiling in general. For the MammaPrint test in particular, there was a published study on the training set (to develop or derive the predictive classifier or model) by Van't Veer and colleagues, and three validation studies to evaluate the predictive accuracy of the model (Van De Vijver 2002, Buyse 2006, and Glas 2006). All studies were reviewed but only the first two validation studies were critically appraised, Glas, et al's study was not selected for critical appraisal due to patient overlap with the van De Vijver study. It is to be noted that Van De Vijver, van't Veer, and several other principal authors are named inventors on a patent application for the 70-gene signature used in the studies. All studies also had financial ties to the manufacturer. *The following studies were critically appraised:*

Van De Vijver MJ, He YD, van't Veer LJ, et al. A gene expression signature as a predictor of survival in breast cancer. N Engl J Med 2002:347:1999-2009. See Evidence Table. Buyse M, van't Veer, L, Viale G et al on behalf of the TRANSBIG Consortium. Validation and clinical utility of a 70-gene prognostic signature for women with node negative breast cancer. J Natl Cancer Inst 2006:98:1183-1192. See Evidence Table.

The use of the MammaPrint test in the treatment of recurring cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

OVA1™ Test for the Assessment of Suspected Ovarian Cancer

BACKGROUND

In the United States, ovarian cancer is the fifth leading cause of all cancer-related death among women. It is estimated that in 2010, there were 21,880 new cases of ovarian cancer and 13,850 deaths from ovarian cancer (Jemal 2010). The incidence of ovarian cancer increases with age with approximately two thirds of cases being diagnosed in women over the age of 55. Women with a family history of ovarian or breast cancer or who are carriers of the BRCA gene mutations are also at increased risk for ovarian cancer (Clarke-Pearson 2009). For patients with early stage disease, survival rates are greater than 90%; however, they are less than 30% for patients with advanced disease. Because of the lack of specific symptoms during the early stage approximately 70% of cases are diagnosed with advanced disease (Carter 2011). The most commonly used tests for the detection of ovarian cancer are transvaginal ultrasound (TVS) and serum CA-125. Recently, the FDA approved the OVA1™ test (Quest Diagnostics, Inc.) to be used as an adjunct to clinical/radiological evaluations for women planning surgery for an adnexal mass. This test measures the serum levels of 5 potential biochemical markers for ovarian cancer (transthyretin, apolipoprotein A1, transferring, CA-125, and β2-mocrogloublin). The results of the test are then interpreted using a proprietary algorithm to yield a single score ranging from 0 to 10 to indicate the likelihood that the adnexal mass is benign or malignant. A high probability for malignancy is defined as a score of at least 5.0 in premenopausal women or 4.4 in postmenopausal women. The goal of the OVA1™ test is to provide additional information to aid in identifying patients who should be referred to a gynecologic oncologist for surgery (Carter 2011, Muller 2010). Studies suggest that women who receive their initial surgical care from an experienced gynecologic oncologist have improved outcomes and greater overall survival. Because of this the National Comprehensive Cancer Network (NCCN) recommends that all patients should undergo surgery by an experienced gynecologic oncologist (NCCN 2011). It is important to emphasize that this test is not approved for ovarian cancer screening and is not intended for use as a standalone test. Another limitation of this test is that assay interference may occur in patients with rheumatoid factor levels of at least 250 IU/mL and triglyceride levels greater than 4.5 g/L (Muller 2010). In 2009, the FDA approved the use of this test for women over the age of 18 with an ovarian adnexal mass for which surgery is planned and have not yet been referred to an oncologist.

10/17/2011: MTAC REVIEW

OVA1™ Test for the Assessment of Suspected Ovarian Cancer

Evidence Conclusion:

Conclusion: Analytic validity: No studies were identified that evaluated analytic validity of the OVA1™ test. Clinical validity: Results from a recent observational study suggest that the when added to physician assessment or substituted for CA 125, the OVA1™ test increased the sensitivity and negative predictive value of these assessments but decrease the specificity and positive predictive value. Clinical utility: No studies were identified that evaluated the clinical utility of the OVA1™ test.

Articles: No studies were identified that assessed the analytic validity or clinical utility of the OVA1™ test. Two studies were identified that addressed the clinical validity of the OVA1™ test. Both of these studies were selected for review. The following studies were selected for critical appraisal: Ueland FR, Desimone CP, Seamon LG, et al.

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Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. *Obstet Gynecol 2011;* 117:1289-1297. See Evidence Table. Ware Miller R, Smith A, DeSimone CP, et al. Performance of the American College of Obstetricians and Gynecologists' ovarian tumor referral guidelines with a multivariate index assay. *Obstet Gynecol.* 2011; 117:1298-1306. See Evidence Table.

The use of OVA1 for ovarian tumors does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Hayes Review

SelectMDx for Prostate Cancer (MDxHealth Inc.)

According to the testing laboratory, the SelectMDx test is a noninvasive, urine-based molecular screening test that, when combined with patient clinical risk factors, can aid physicians in determining if a patient is at higher risk (defined by laboratory as detecting GS ≥ 7 prostate cancer upon biopsy) or lower risk for prostate cancer and can avoid biopsy (MDxHealth, 2019a). The test is intended for men who have not been previously diagnosed with prostate cancer. The SelectMDx test requires a first void post-digital rectal examination (DRE) urine sample, which is analyzed for the mRNA level of 2 cancer-related biomarkers, DLX1 and HOXC6 (MDxHealth, 2016; MDxHealth, 2019b).

Hayes Rating: D2

For use of the SelectMDx for Prostate Cancer test to aid physicians in determining if a patient is at higher risk (defined by laboratory as detecting Gleason score (GS) ≥ 7 prostate cancer upon biopsy) or lower risk for prostate cancer and can avoid biopsy.

Conclusion: There is insufficient evidence supporting use of the SelectMDx test. Additional studies are needed to demonstrate the clinical validity and, ultimately, clinical utility of the test and whether the test results would improve patient management outcomes, including avoiding unnecessary prostate biopsies.

Reference

Hayes. Hayes Molecular Test Assessment. SelectMDx for Prostate Cancer (MDxHealth Inc.). Dallas, TX: Hayes; February 25, 2021. Retrieved November 29, 2021 from https://evidence.hayesinc.com/report/gte.selectmdx3769

Thyroid Nodule Gene Expression Testing (Afirma)

BACKGROUND

Thyroid nodules are very common; they are clinically identified in 5-7% of the population, and incidentally on ultrasonography in up to 50% of women and 20% of men over the age of 50. The thyroid nodules are typically benign, but 5-15% prove to be malignant. It is thus recommended that any identified nodule measuring one centimeter or more in diameter be diagnostically evaluated. Thyroid fine needle aspiration (FNA) biopsy is the most widely used method for clinical evaluation of a suspicious thyroid nodule. FNA is a safe and simple outpatient procedure that yields cellular material suitable for cytological analysis. However, 15-30% of the biopsied nodules has indeterminate cytology and cannot be conclusively diagnosed by FNA biopsy alone. Most patients with indeterminate lesions (defined in the Bethesda System as Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance, suspicious for Follicular or Hurthle Cell neoplasm and suspicious for malignancy) are referred to surgery. Currently, surgery is performed for both diagnostic and therapeutic purposes in these patients with indeterminate aspirates. Surgery has high operative efficacy in removal of thyroid cancer, however approximately three-quarters of the nodules with indeterminate FNA cytology are ultimately found to be benign on final surgical pathology. Thus, a large proportion of patients with indeterminate nodules may undergo unnecessary partial or complete thyroidectomy with its potential surgical complications and risk of long-term morbidity (Alexander 2012, Duick 2012, Walsh 2012, Ali 2013). In an attempt to preoperatively classify the indeterminate thyroid nodules different novel diagnostic tests and molecular markers have been investigated. These include immunohistochemistry, mutation and gene rearrangement testing, and gene expression and microarray analysis. Each has its performance characteristics and diagnostic values. Ideally a molecular marker or panel of markers would be accurate in differentiating benign from malignant in any lesion that is considered suspicious or indeterminate. It should be simple to use, reproducible by all institutions, and cost-effective. Genetic markers associated with malignancy such as mutation markers (e.g. BRAF, RAS) and gene rearrangements (e.g. RET/PTC and PAX8-PPAry) have high specificity and positive predictive values; and when detected they can “rule in” the diagnosis of thyroid cancer, However, they have limited sensitivity and negative predictive values as they fail to detect a large proportion of malignant samples that do not contain one of the mutations or rearrangements being tested, i.e. mutation or rearrangement markers cannot ‘rule out’ malignancy when not detected (Alexander 2012, Kouniavsky 2012, Ward 2013). Microarray techniques seek to identify patterns of expressed RNA in the human

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genome that are predictive of benign or malignant thyroid disease. Unlike single gene mutations or rearrangements, microarray diagnostic tests involve tens to hundreds of expressed genes. The currently available diagnostic microarray for use in thyroid nodule analysis is the Afirma Gene Expression Classifier (GEC) recently developed by Veracyte, Inc. It is a genomic test designed with the intention of preoperative identification of benign thyroid nodules in patients with indeterminate FNA cytopathological results. The test assesses gene expression from mRNA isolated from thyroid FNA samples by comparing the mRNA expression detected in a thyroid FNA against a panel of 167 molecular genes. It uses a multidimensional algorithm to identify the thyroid FNA samples with a benign gene expression pattern (Alexander 2012, Kim 2012, Ward 2013). Afirma GEC is commercially owned by Veracyte Corporation; South San Francisco, California and is offered through a sole source, Clinical Laboratory Improvement Amendments (CLIA), a certified reference laboratory. Afirma CEC analysis is indicated only for nodules with indeterminate cytology, and is not performed on cytologically benign, malignant, or nondiagnostic (insufficient FNA samples) nodules. The assay classifies nodule as either benign or suspicious for malignancy. With a preoperative identification of a nodule that is benign rather than malignant, observation or ultrasound follow-up could be recommended instead of thyroid surgery, i.e. potentially avoids unnecessary surgery (Alexander 2012, Duick 2012, Ward 2013).

10/21/2013: MTAC REVIEW

Thyroid Nodule Gene Expression Testing (Afirma)

Evidence Conclusion: Analytic validity Evaluating the analytic performance of Afirma GEC includes studying the stability of RNA in FNAs during collection, storage, and shipment; reproducibility of the test; and its analytic sensitivity and specificity under various conditions e.g. interference of the assay with bloody FNA and genomic DNA. The literature search revealed one study (Walsh and colleagues, 2012) that evaluated the analytic performance of Afirma GEC in a number of sub studies. The investigators obtained prospective FNA samples aspirated in vivo from 43 patients from outpatient clinics, preoperatively, or immediately after surgical excision. The samples were placed in FNAProtect preservative solution and shipped chilled or frozen, then stored at -80^{o}C upon receipt. The RNA was extracted, and its yield examined for quantity and quality using positive (tissue lysate) and negative (water) as controls. Three different lots of controls were tested over several weeks of independent runs by 3 different operators to determine reliability of the test. Multiple lots of benign and malignant total RNA were manufactured and used as process controls to determine the analytic sensitivity of the test using different RNA input quantity and under different dilution of malignant FNA content. These studies indicated tolerance to variation in RNA input across a range of 5-25 ng. as well as dilution of malignant FNA material down to 20%. Analytic specificity of the test using malignant samples mixed with blood (up to 83%) and genomic DNA (up to 30%) showed minimal assay interference. However benign FNA samples mixed with relatively high proportions of blood had a potential for yielding false positive results. The authors also examined the stability of RNA in FNAs during collection and shipment and found that RNA content within FNAs preserved in FNAProtect was stable for up to 6 hours at room temperature with no change in RNA yield, and that the FNA storage and shipping temperatures had no significant effect on GEC scores. They also examined the reproducibility of the test and indicated that it was reproducible from extraction through GEC results, including variation across operators, runs, reagent lots, and laboratories. The authors concluded that the analytical performance and reproducibility of the Afirma Gene Expression Classifier was successfully verified. The research was supported by Veracyte Corporation, (the maker of Afirma GEC), and the authors of the study were either employed by or were consultants to the corporation. Clinical validity A perfect test would have high sensitivity and high specificity in correctly detecting or excluding a condition. A molecular diagnostic test with high sensitivity offers a high negative predictive value when the risk of malignancy (ROM) is low and can “rule out’’ malignancy. Conversely, a test with high specificity offers high positive predictive value and can “rule in” cancer. To be of use in avoiding surgery, a test that better distinguishes benign from malignant nodules needs to have high sensitivity and high negative predictive value. The literature search identified two published studies on the validation of Afirma GEC (Chudova et al, 2010, and Alexander et al. 2012); both funded by Veracyte Corporation the maker of Afirma GEC. The more recent and larger validation study by Alexander and colleagues (evidence table 1), was a double-blind prospective multicenter validation study. 4,812 thyroid FNAs were obtained from 3,789 patients. 577 (12%) samples were classified as indeterminate, and less than half (46%) were ultimately selected for GEC analysis. Molecular results were compared to the gold standard of post-surgical histopathology interpreted by a panel of blinded endocrine histopathologists for clinical validation. The overall sensitivity of the Afirma test was 92% with a negative predictive value (NPV) of 93% (95% for atypical or follicular lesions of undetermined significance (AUS/FLUS), 94% for a follicular neoplasm, and 85% for a lesion suspicious for malignancy). It is to be noted that the predictive values of a test vary with the prevalence of the disease in the population studied and may not be generalized to other groups. A better analysis would be the likelihood ratios which are not affected by prevalence. Seven of the 85 (8.2%) overall cancers were diagnosed incorrectly by the GEC as benign (false negative). The authors attributed the false negative results to insufficient RNA in the FNA sample used for GEC. The test had an overall low specificity and positive predictive values (52% and 47% respectively). Atypical or follicular lesions of undetermined significance (AUS/FLUS) accounted for almost

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50% of the indeterminate thyroid FNAs samples. 43% of these FNA were reclassified with the GEC as benign and 57% remained in their suspicious category. Other investigators showed that repeat FNAs without a molecular test can also accurately reclassify >50% of the nodules in the AUS/FLUS category as benign (Faquin 2013). The study was conducted to validate the GEC accuracy by comparing it to surgical histopathology, and the authors did not compare its performance to repeat FNA or other immunochemical testing. Clinical utility: The clinical utility of Afirma GEC was evaluated in a retrospective study by Duick and colleagues, 2012, (Evidence table 2). They obtained their data from 21 endocrinology practices in 11 states. The authors conducted a chart review of 368 patients with 395 cytologically indeterminate thyroid nodules that were GEC benign. 7.6% of these patients with Afirma GEC benign nodules underwent surgery and 94.4% were managed nonoperatively. The study did not have a comparison group, but the authors compared the 7.6% surgical rate to a 74% historical rate of diagnostic surgery (P<0.001). The indications for surgery for those with GEC benign results included a large size or rapid growth of the nodules, local pressure symptoms, or the presence of a second suspicious nodule or malignant nodule. The authors explained that these were similar to indications for surgery on nodules with benign FNA cytologically. The study was retrospective, used a historical comparison, and investigated the decision-making of endocrinologists experienced in managing patients with thyroid nodules, which may differ from that made by primary care providers or other specialists. In addition, the authors of the study did not provide data on long-term follow-up of those who were managed by watchful waiting rather than surgery. In conclusion, there is insufficient evidence to determine whether Afirma GEC is more accurate than repeat FNA or immunochemical testing in reclassifying cytologically indeterminate thyroid nodules. There is also insufficient evidence to determine the impact of Afirma GEC on clinical management and net health outcomes in patients with indeterminate thyroid nodules.

Articles: The literature search for gene expression classifier for preoperative identification of benign thyroid nodules with indeterminate fine needle aspiration cytopathology revealed a number of articles on molecular diagnostic tests. Many were reviews, editorials, letters, or were unrelated to the current review. The search identified a study on the analytic validity of the test, two on its clinical validity, and retrospective study on its clinical utility. The following studies were selected for critical appraisal. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med*. 2012; 367:705-715. See Evidence Table Duick DS, Klopper JP, Diggans JC, et al. The impact of benign gene expression classifier test results on the endocrinologist-patient decision to operate on patients with thyroid nodules with indeterminate fine- needle aspiration cytopathology. *Thyroid.* 2012 22:996-1001. See Evidence Table

The use of does Afirma® Thyroid FNA Analysis (Gene Expression Classifier) for Thyroid Nodules with Indeterminate Fine Needle Aspiration Cytopathology not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

ConfirmMDx for Prostate Cancer

BACKGROUND

Prostate cancer is the second most leading cause of cancer in men around the globe (Fitzmaurice et al., 2017). In the United States, one in six men has a lifetime risk of prostate cancer (Siegel, Ward, Brawley, & Jemal, 2011). Prostate cancer screening is subject to controversy due to overdiagnosis, overtreatment, and harms. Major guidelines highlight the importance of informed decision-making. Despite the controversy, prostate specific antigen (PSA) and or digital rectal examination (DRE) can be performed.

After undetermined or abnormal results are reported on prostate cancer screening, more tests such as prostate biopsy is indicated for prostate cancer diagnosis. A high proportion (62%) of initial biopsies are negative and up to 43% will have second/repeat biopsies. Of these repeat biopsies, 26% – 35% will be diagnosed with prostate cancer (Auprich et al., 2012). False negative results are non-negligible since biopsy can miss cancer (Bhindi et al., 2017). In addition, prostate biopsies may result in several complications. As a result, it is crucial to find other ways to avoid or decrease repeat biopsies and predict with accuracy prostate cancer in patients with negative initial biopsies. ConfirmMDx is an assay that evaluates molecular alterations of three genes to detect prostate cancer.

The following description of the test is from the manufacturer website (https://mdxhealth.com/confirmmdx-physician/). ConfirmMDx is a tissue test to enhance the detection of previously negative biopsy patients at high risk for clinically significant prostate cancer. It rules out patients with no cancer and prevent them from unnecessary repeat biopsies and screening procedures, thus alleviating stress and reduce complications. According to the manufacturer, ConfirmMDx is believed to be the most significant predictor of patient outcome among all currently available clinical factors.

ConfirmMDx uses methylation-specific PCR (MSP) and epigenetic biomarkers to detect prostate cancer. The MSP, unlike histopathology, can detect DNA methylation changes (molecular alterations) in tissues surrounding cancer foci. This epigenetic effect is the molecular mechanism by which MSP detects occult prostate cancer in men with negative

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initial biopsy. ConfirmMDx measures DNA methylation of 3 genes including GSTP1, APC, and RASSF1. In patients with negative prostate biopsies results, the test can enhance accuracy for predicting repeat biopsy outcome in comparison to the standard risk factors (Waterhouse et al., 2019). The test can also indicate the likelihood of detecting Gleason score ≤ 6 (low grade) and ≥7 (high grade) prostate cancer upon repeat biopsy. Patient report indicates if DNA methylation is positive, the likelihood of detecting prostate cancer, probability of detecting Gleason score ≤ 6 and ≥7 prostate cancer on repeat biopsy (https://mdxhealth.com/wp-content/uploads/2020/07/MDX-C152-ConfirmMDx-Case-Study-1-v3.pdf).

The test is indicated when there is a need to perform repeat biopsy on patients with initial negative biopsy result (benign, high-grade prostatic intraepithelial neoplasia (HGPIN), or atypical small acinar proliferation (ASAP)) within the past 24 months and high-risk clinical factors for occult prostate cancer. The results of the test should be interpreted in addition to clinical and other laboratory data.

Eligible patients include those with the following biopsy results:

- Negative/benign
- HGPIN (high-grade prostatic intraepithelial neoplasia)
- Atypia (atypical glands suspicious for malignancy)
- ASAP (atypical small acinar proliferation)
- PIA (proliferative inflammatory atrophy, or lesion)

07/11/2022: MTAC REVIEW
ConfirmMDx for Prostate Cancer
Evidence Conclusion:

- Analytical validity: Very low-quality study shows that the assay can measure the methylation status of the three genes including GSTP1, APC, and RASSF1.
- Clinical validity: Low quality evidence support ConfirmMDx in ruling out prostate cancer on repeat biopsy.
- Clinical utility: There is insufficient evidence for or against the clinical utility of ConfirmMDx for prostate cancer.
- **Overall, the evidence is insufficient for or against the use of ConfirmMDx.**

Articles: PubMed was searched on 03/29/2022 with the search terms ConfirmMDx OR Episcore OR MDxHealth OR (GSTP1 AND APC AND RASSF1 AND prostate) OR (Epigenetic assay AND prostate cancer) with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded a number of articles. Seven studies were reviewed (1 analytical validity study, 4 clinical validity studies, and 2 clinical utility studies). See Evidence Table.

The use of ConfirmMDx for Prostate Cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Hayes Review

ConfirmMDx for Prostate Cancer (MDxHealth Inc.)

According to the laboratory, ConfirmMDx is for men with a previous histopathologically cancer-negative prostate biopsy within the past 24 months who have clinicopathological risk factors for prostate cancer to (MDxHealth, 2017; MDxHealth, 2018a):

- Identify men at risk for undetected prostate cancer (a false-negative biopsy result).
- Rule out men who are prostate cancer free to prevent unnecessary repeat biopsies and screening procedures, resulting in reduced complications, patient anxiety, and healthcare expenses.

In addition, the ConfirmMDx test result claims to predict the likelihood of (MDxHealth, 2017):

- Detecting Gleason score ≤ 6 prostate cancer on repeat biopsy.
- Detecting Gleason score ≥ 7 prostate cancer on repeat biopsy.

Hayes Rating: **D2**
For use of ConfirmMDx test, using residual prostate biopsy specimens, to: (1) rule out men who are prostate cancer free; and (2) identify men at risk for undetected prostate cancer by predicting the likelihood of detecting Gleason score ≤ 6 and ≥ 7 prostate cancer on repeat biopsy in men with an initial negative biopsy yet high-risk

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clinicopathological features suggestive of prostate cancer.

Conclusion: There is positive but insufficient evidence supporting the use of the ConfirmMDx test to help rule-out prostate cancer in repeat biopsy and insufficient evidence for the use of the test to predict the likelihood of Gleason score ≤ 6 prostate cancer and Gleason score ≥ 7 prostate cancer on repeat biopsy. Available studies do not evaluate whether the test results, when used to influence patient repeat biopsy decisions, result in improved patient outcomes in men with high-risk clinicopathological features suggestive of prostate cancer.

Reference

Hayes. Hayes Molecular Test Assessment. ConfirmMDx for Prostate Cancer (MDxHealth Inc.). Dallas, TX: Hayes; February 14, 2021. Retrieved November 29, 2021 from https://evidence.hayesinc.com/report/gte.confirm2766

Prolaris for Prostate Cancer

BACKGROUND

Prostate cancer is the second most leading cause of cancer in men around the globe (Fitzmaurice et al., 2017). In the United States, one in six men has a lifetime risk of prostate cancer (Siegel, Ward, Brawley, & Jemal, 2011). Its natural history varies and is difficult to predict. Some men have indolent disease that can be safely managed with active surveillance, whereas others have an aggressive cancer and are treated with a variety of therapeutic options. Accurate prediction of disease behavior is critical because radical treatment is associated with high morbidity (J. Cuzick et al., 2012).

Clinical variables including Gleason score, tumor stage, and PSA have been considered at the time of diagnosis to predict disease outcome. However, predictions based on these variables are not accurate, resulting in hesitation among physicians and patients about the best course for initial treatment (J. Cuzick et al., 2012). Tests to make accurate prediction and determine treatment decision are necessary.

Description:

Prolaris is a genetic test that measures the growth of tumor cell. In combination with PSA and Gleason score, the test determines the aggressiveness of prostate cancer. PSA and Gleason only show the progression of prostate cancer. However, when these tests are combined to Prolaris test, the aggressive progression of the cancer over the next ten years is determined. The information on the aggressiveness of cancer is specific to each individual.

Testing process:

The same tissue from the original biopsy is utilized to run the test. Therefore, additional biopsies are not required. The tissue sample is sent to Myriad to determine the aggressiveness of the prostate cancer. After the test is complete, the results are sent back to the provider. The result is comprised of a personalized Prolaris Score and a 10-year prostate cancer mortality risk and the risk of metastasis.

The Prolaris Molecular Score is computed by measuring the expression of 31 cell cycle progression (CCP) genes (measured by qRT-PCR and normalized by 15 housekeeping genes). Most of the scores range between 1-11. The higher the score, the more aggressive the cancer. Over- and under-expression of the 31 CCP genes results in positive and negative CCP score, respectively (Shangguan et al., 2021).

Benefits of Prolaris test:

The benefits are to identify mortality risk, the risk of metastasis, and to help determine the best course of treatment.

Prolaris is supported by NCCN guidelines as a 2A recommendation which is considered standard of care. Prolaris testing is indicated in men who have been diagnosed with localized prostate cancer.

07/11/2022: MTAC REVIEW
PROLARIS FOR PROSTATE CANCER
Evidence Conclusion:

- **PROLARIS BIOPSY TEST**
  - Low quality evidence shows that CCP testing is reproducible and precise.
  - Very low to low quality evidence indicate that CCP & CCR scores may help predict prostate cancer mortality and metastasis. It may help improve risk stratification in men with localized prostate cancer.
  - Low quality evidence shows that Prolaris test may influence physician treatment decision.
  - Overall, low quality evidence supports Prolaris test to predict prostate cancer related clinical outcomes.

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➢ **PROLARIS POST-PROSTATECTOMY**

- The evidence is insufficient for or against the use of Prolaris test in patients with radical prostatectomy.

Articles: PubMed was searched through April 11, 2022 with the search terms (Prolaris OR cell cycle progression OR CCP OR cell cycle risk OR CCR) AND (prostate) with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. ***See*** **Evidence Table.**

The use of Prolaris Prostate Cancer (Biopsy and Post-Prostatectomy) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/20/2015: MTAC REVIEW
DecisionDx - Melanoma
Evidence Conclusion:
DecisionDx - Melanoma
BACKGROUND
Skin cancer is extremely common accounting for nearly half of all cancers in the United States. Melanoma, the most aggressive type of skin cancer, occurs as a result of abnormal melanocytes, most often caused by over- exposure to ultraviolet radiation from the sun. When detected early, cutaneous melanoma can be surgically excised resulting in a 5-year overall survival rate of 91%-97%. Despite these odds, however, the clinical behavior of cutaneous melanoma is highly variable and some melanomas, that appear less risky, will develop into advanced disease and require extensive treatments such as additional surgery, immunotherapy, targeted therapy, chemotherapy and radiation therapy (ACS 2015). As with all cancers, a primary challenge is predicting prognosis. Conventional methods of melanoma staging are characterized by the American Joint Committee on Cancer (AJCC) TNM System. The TNM system specifically refers to Tumor thickness, spread to nearby lymph Nodes, and Metastasis. Based on history and physical exam, as well as, biopsy, imaging and pathology, the TNM system groups patients with melanoma into stages, 0-IV based on the advanced nature of the disease (Balch, Gershenwald et al. 2009). The stage of the melanoma is an estimate of prognosis and will ultimately guide treatment options. Recently, gene expression profiling (GEP) has been proposed for use in cancer management. The technique specifically analyzes the patterns of genetic material contained in tumor cells and has the potential ability to predict clinical outcomes associated with cancer. One such test, the DecisionDx-Melanoma™, developed by Castle Biosciences Inc. (Friendswood, TX), is described to more accurately classify stage I and II melanoma.
Proposed as an adjunct to conventional staging systems, the DecisionDX-Melanoma test includes 31 genes, 28 of which have previously been associated with melanoma and the remaining three, controls (Winnepenninckx, Lazar et al. 2006). The results of the DecisionDx-Melanoma test is further claimed to stratify stage I and II melanomas into one of two classes; class one identifying patients as low risk of metastasis, or class two indicating high risk.
The developer claims that the information provided by the DecisionDx-Melanoma test enables physicians to tailor, patient specific, surveillance and treatment plans informing, for example, the intensity of surveillance, need for referral to specialists, evaluation of adjuvant treatments and clinical trial eligibility (CastleBiosciencesInc. 2015).

04/20/2015: MTAC REVIEW
DecisionDx - Melanoma
Evidence Conclusion: The study aimed to develop a prognostic genetic signature based on previous analyses of cutaneous melanoma tumors. To do this, the investigators included 268 archived tissue samples and divided the sample into two cohorts, development (n=164) or validation (n=104). The investigators compared the patient clinical outcomes at five years with the GEP test prediction. Overall, Kaplan-Meier analysis indicated that the five-year disease-free survival (DFS) rates in the validation cohort were 97% and 31% for predicted class 1 and 2, respectively ($p<0.0001$). These results were comparable to the DFS rated in the development cohort, 100% and 38% for class 1 and class 2, respectively ($p<0.0001$). The investigators ultimately concluded that in patients with primary cutaneous melanoma, the GEP signature accurately predicts metastasis risk (Gerami, Cook et al. 2015). [Evidence Table 1] The investigators had the clear intent to develop and validate a GEP for predicting metastatic risk in stage I and II cutaneous melanoma. The patient sample was well defined and the study design, cohort, appeared to be appropriate for the development of the genetic signature. To validate the test, however, the study relied on archived tumor samples with at least five years of follow-up. While this is a sufficiently long time to detect the outcome of interest, and the investigators used an independent sample, a prospective study would be a more appropriate design for validation. With that said, the investigators report that samples were collected at a similar point in the course of the disease, diagnosis, however the diseases progression at diagnosis may have varied between patients and it is not clear if the investigators were blinded to prognostic factors. On a final note, the study was funded by the test manufacturer and at least two of the investigators have financial ties with Castle

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Biosciences, Inc. Conclusions: There is limited evidence to conclude that the DecisionDx-Melanoma test is valid. There is insufficient evidence to conclude that the DecisionDx-Melanoma test has prognostic accuracy in predicting metastatic risk. There is insufficient evidence to conclude that the DecisionDx-Melanoma test is not harmful to patients. There is insufficient evidence to establish the clinical utility and therapeutic impact of the DecisionDx-Melanoma test.
Articles: The literature search was carried out to identify studies relating to the prognostic value of the DecisionDx-Melanoma test. The search revealed a variety of publications discussing the use of GEP and one publication identifying the genes associated with melanoma progression and prognosis (Winnepenninckx, Lazar et al. 2006). No studies were identified in which the DecisionDX-Melanoma was prospectively analyzed and followed- up in populations with Stage I and II melanoma. A search of the NIH Clinical Trials database identified two manufacturer sponsored prospective studies currently in the enrollment stage. The best, currently available, evidence was a development and validation study published by Castle Biosciences, Inc. The following articles were selected for critical appraisal: Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. Clinical Cancer Research. 2015:21(1);175-183. See Evidence Table.

The use of DecisionDx-Melanoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

OVA1 Assessment for Ovarian Cancer

BACKGROUND

Ovarian cancer is the most lethal gynecological malignant worldwide. The five-year overall survival is over 90% in patients with stage I disease and only 20-40% for stages III and IV. Unfortunately, because of the lack of specific symptoms during the early stage approximately 70% of cases present with an advanced stage disease. Detection of ovarian cancer at an early stage would have a significant impact on reducing mortality, however to date; there is no screening or biomarker test that meets the criteria for a beneficial screening test in asymptomatic women with early ovarian cancer (Carter 2011, Cohen 2014, Leung 2014). Serum CA-125, a high molecular weight glycoprotein, remains the most widely used biomarker for the confirmation of diagnosis and management of ovarian cancer. Serum CA-125 however, is more prominently expressed in patients with late stage serous tumors; it is elevated in 50-60% of women with stage I epithelial ovarian cancer, and in 75-90% of patients with advanced stage disease. Elevated circulating CA-125 has also been documented in uterine fibroids, endometriosis, pregnancy, menstruation, benign ovarian neoplasms, liver cirrhosis, and other malignancies making it a less useful marker for the detection of ovarian cancer (Autelitano 2012, Cohen 2014). Improvements have been made in the preoperative diagnosis of ovarian cancer by combining serum CA-125 concentration with ultrasound score and menopausal status, into a Risk of Malignancy Index (RMI) which was found to outperform CA-125 alone in discriminating between a benign and malignant pelvic mass. Over the past two decades diagnostic triage methods incorporating clinical algorithms, serum biomarkers, imaging, or a combination of these techniques have been investigated to improve its diagnostic efficiency in predicting ovarian malignancy in women with adnexal masses. The Risk of malignancy Algorithm (ROMA) and OVA1 test are two algorithms recently developed for the assessment of malignancy risk in these women. These are not screening tests but are potential tools to further triage women to the appropriate provider once the decision for surgical intervention has been made (Autelitano 2012, Bristow 2013, Cohen 2014). Combining multiple variables or markers in a single biomarker assay (in vitro diagnostic multivariate assay [IVDMIA, or MIA]) has the potential advantage of complementing the information provided by a single-valued index. The inclusion of biomarkers in an IVDMIA requires that they are complementary and collectively outperform a single marker with respect to its intended uses. CA-125 remains the best tumor marker, and the selection of additional biomarkers is based mainly on their ability to detect malignancy in cancer patients with low CA-125 level or to reduce false positive results among non-cancer patients with elevated serum CA-125 levels (Zhang 2012). Ova1™ test (developed by Vermillion and licensed to Quest Diagnostics, Inc.) is the first IVDMIA of protein biomarkers cleared by the FDA to be used as an adjunct to clinical and radiological evaluations for women over the age of 18 who have planned to undergo surgery for an adnexal mass and have not been referred to a gynecologic oncologist. Studies suggest that women who receive their initial surgical care from an experienced gynecologic oncologist are more likely to have better outcomes including surgical staging, optimal debulking, and improved median and overall-5-year survival. Ova1™ test is a qualitative test that measures the serum levels of 5 potential biochemical markers for ovarian cancer (CA-125, prealbumin, apolipoprotein A-1, β2-microgloublin, and transferrin). The results of the test are then interpreted using a proprietary algorithm to yield a single score ranging from 0 to 10 to indicate the likelihood that the adnexal mass is benign or malignant. A high probability for malignancy is defined as a score of ≥ 5.0 in premenopausal women or ≥ 4.4 in postmenopausal women. The decision for selecting these cutoff values was made to emphasize the need for high sensitivity to minimize the risk of false negative results for patients who actually have a malignant lesion. A limitation to OVA1™ is that all the included markers with the exception of CA-125 are acute phase reactants that may be nonspecific for ovarian cancer. Another limitation is interference of triglyceride levels greater than 4.5g/L or

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rheumatoid factor levels more than 250IU/mL with the biomarkers assay (Muller 2010, Carter 2011, Zheng 2012, Leung 2014).

04/20/2015: MTAC REVIEW

OVA1 Assessment for Ovarian Cancer

Evidence Conclusion: The main purpose of adding biomarkers to an established tumors biomarker as CA-125, in a multivariate index assay (MIA), is to achieve a very high sensitivity without sacrificing the specificity. However, the published studies evaluating OVA1™ showed the test improved the sensitivity of the physicians' assessment in predicting ovarian malignancy in women with adnexal masses, but at the cost of reducing the specificity and positive predictive value. The FDA cleared the OVA1™ test based on the results of Ueland and colleagues' study that was reviewed earlier by MTAC in 2011. The study compared the sensitivity, specificity, and predictive values of physician assessment with or without adding the multivariate index assay (MIA) in identifying high-risk ovarian tumors. The study enrolled 590 women (524 evaluable with both MIA and CA-125-II) with a documented ovarian mass on imaging and planned surgery within 3 months of imaging. 53% of the women were enrolled by non-gynecologic oncologists and the rest by gynecological oncologist. The MIA index assay test was performed on preoperative serum samples, and the results were correlated with preoperative physician assessment. There was no specific protocol for the clinical assessment. Using surgical pathology as the gold standard, 161 women were diagnosed with a malignant and 363 with a benign ovarian tumor. The results of the analysis showed that the sensitivity of non-gynecologic oncologists' assessment increased from 72% to 92% with the addition of the MIA test (78% and 99% respectively for gynecologic oncologists). The negative predictive value increased slightly with the addition of the MIA test. On the other hand, the specificity and positive predictive values dropped significantly with the addition of the assay (the specificity was reduced from 83% to 42% for non-gynecologic oncologists and from 75% to 26% for gynecologic oncologists and the positive predictive value dropped from 60% to 36% and from 63% to 43% in the two groups of respectively).The studies published after that pivotal study were conducted mainly by the same group of investigators who either analyzed the results of women enrolled in some or all 44 sites participating in the study. The studies were sponsored by Vermillion Inc., and the investigators had financial ties to the company. The largest and most recent of these studies (Longoria et al 2014) (Evidence table 1) compared the accuracy and predictive values of the multivariate index assay, OVA1™ to clinical assessment, CA-125-II, and the modified American Congress of Obstetricians and Gynecologists (ACOG) guidelines, for the detection of early-stage ovarian cancer in 1,016 women undergoing surgery for an adnexal mass. The authors did not indicate whether the assessors were blinded to the other tests and/or clinical evaluation results. The study did not include women without adnexal masses or with other disorders that may lead to elevated levels of CA-125 or any of the other biomarkers included in the assay. Overall, similar to the Ueland and colleagues' study, as well as the other published studies using MIA test, Longoria, et al's study showed that the addition of OVA1™ to clinical assessment may significantly improve the sensitivity of detecting early-stage ovarian cancer, but at the expense of reducing the specificity, which would result in referral of more patients with benign conditions to gynecologic oncologists for surgery. The overall results of the study show the following: ***Comparative performance for evaluable women in all cancer cases (from evidence table 1)***

	Sensitivity %	Specificity %	PPV %	NPV %
OVA1	92.2%	49.4%	37.9%	94.9%
Clinical assessment*	74.5%	86.3%	64.6%	91.0%
OVA1 + clinical assessment	95.3%	44.2%	36.4%	96.6%
CA 125-II	70.6%	89.6%	69.5%	90.1%
Modified ACOG guidelines**	80.0%	76.5%	53.3%	91.9%

*The authors did not clearly explain that clinical assessment included CA125-II for all women

** Included: very elevated CA125 (>67U/mL), ascites, and evidence of abdominal or distant metastasis for premenopausal women. For postmenopausal women the ACOG criteria were Elevated CA125 (>35 u/mL, nodular or fixed pelvic mass, ascites, and evidence of abdominal or distant metastasis.

The studies had enrolled selected groups of women with adnexal masses who were referred to surgery in multiple centers with no standardized process for data collection or referral practice. The referral pattern was retrospectively analyzed, and the impact of the test on health outcomes was not evaluated. In addition, the studies were funded by Vermillon Inc, the developer of the test, and the principal investigators had financial ties to the company. The performance of OVA1™ was not compared to other risk assessment algorithms as ROMA,

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ultrasound-based risk assessment models, or other diagnostic tools that may lead to similar sensitivity and superior specificity to OVA1™. Conclusion: The published studies do not provide sufficient evidence to determine the clinical utility and impact of using OVA1™ assay on health outcomes of women with ovarian tumors.

The use of OVA 1 does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Date: 07/09/2018 MTAC REVIEW

Whole Genome/Exome Sequencing for Developmental Delay (DD)/Intellectual Disability (ID)

BACKGROUND

Intellectual disability is a disorder marked by deficits in intellectual and adaptive functioning and starts before 18 years of age. Its management requires early diagnosis and extensive supports. Intellectual disability is caused by any conditions disrupting brain development. Of these conditions, genetic abnormalities are the most commonly known etiologies (Rauch et al., 2012) with Down syndrome being the leading cause. Conventional cytogenetics (karyotype analysis and fluorescence in situ hybridization (FISH)) can identify the cause but they detect less than 10% of chromosomal abnormalities in patients with intellectual disability (ID) or developmental delay (DD) (Shaffer, Beaudet, et al., 2007; Shaffer, Bejjani, et al., 2007). Chromosomal microarray analysis (CMA) has become the primary test for most patients with intellectual disability (Miller et al., 2010). However, if CMA fails to identify the etiology, whole genome/exome sequencing may be considered.

Whole genome sequencing (WGS) is a process that determines the complete DNA sequence of the entire genome. In contrast, whole exome sequencing (WES) determines the DNA sequence of a small part of the genome. The small part which is the coding part of the genome is 1% of the entire genome.

(Biesecker & Green, 2014) Genome and exome sequencing (GES) begins with extraction of DNA from white cells followed by disintegration of DNA and determination of sequences with sequencing instrument. Using computer, the sequences are placed into specific positions in the human genome reference sequence for assessment of similarities and differences. This results in the determination of the specific genotype at each position in the exome or genome. This leads in output file which is filtered for variants that explain the phenotype. Sequencing can be performed on unaffected or affected parents or affected siblings. Clinical GES can detect single-nucleotide substitutions and insertions or deletions of 8 to 10 nucleotides or smaller. However, it is less accurate for other types of genomic variation. GES is indicated in patients with suspicion of mendelian genetic disease. It is also considered when CMA fails to identify the cause of intellectual disability. (Biesecker & Green, 2014)

This review focuses on developmental delay (DD) or intellectual disability (ID).

As this is a laboratory test, no FDA approval is required. Genetic tests are controlled under the Clinical Laboratory Improvement Amendments (CLIA). The technology is being assessed for the first time on Medical Technology Assessment Committee (MTAC).

Evidence Conclusion:

Conclusion:

- **Analytical validity:** Studies assessing analytical validity were scarce. Only two studies reported that the performance of WES/WGS was high. However, the evidence is insufficient to draw conclusion on analytical validity.
- **Clinical validity:** Thirteen studies were evaluated. Most studies have included children with moderate to severe intellectual disability/developmental delay. In most studies, WES or WGS was performed in patients on whom previous genetic evaluations (molecular karyotyping, microarray) failed to diagnose the etiology or were negative. The diagnostic yield ranged from 21% to 60% (including new mutations) suggesting higher detection rate than traditional genetic tests including microarray. Nevertheless, the studies provide low evidence and demonstrate that WES/WGS has high detection rate overall and even in children with undiagnosed or unexplained intellectual disability or developmental delay.
- **Clinical utility:** The evidence on clinical utility is conflicting. More studies are warranted.
- Milliman Care Guidelines was reviewed and indicated that the evidence is poor, or conflicting, or insufficient to assess the net benefit of this test versus harm; additional research is recommended.

The use of Whole Genome/Exome Sequencing for Developmental Delay (DD)/Intellectual Disability (ID) doesn't meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Next Generation Sequencing (NGS) - Broad Spectrum Tumor Molecular profiling

Background

All cancers begin in cells. A normal become cancerous largely because of mutations in their genes. Often many mutations are needed before a cell becomes a cancer cell. Some gene changes may increase production of a protein that makes cells grow and others may result in the production of a misshape leading to a nonfunctional

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form of a protein that normally repairs cellular damage. Genetic changes that promote cancer may be inherited (germline) or more commonly acquired (somatic) during a person's lifetime, either because of errors that occur as cells divide or from exposure to DNA-damaging carcinogens. There are many types of DNA genetic changes; these may affect just one unit of DNA (a nucleotide) or involve larger stretches of DNA (NIH, American Cancer Society).

Somatic mutations include point mutations, small insertions/deletions, and copy-number alterations that direct therapeutic options. Thus, in some cases, knowledge of the genetic alterations in a cancer patient can help determine a treatment plan as some treatments, particularly targeted therapies, are effective only for people whose cancer cells have specific genetic alterations that cause the cells to grow out of control (Wagle 2011, National Cancer Institute).

In the past decade, investigators have focused on searching for oncogenes and tumor suppressor genes that drive cancer. This is moving systemic cancer treatment away from the paradigm of treating histologically defined disease with cytotoxic chemotherapy, towards the use of molecularly targeted drugs prescribed to selected subsets of patients across multiple tumor types. Theoretically targeted therapies that inhibit the abnormally activated proteins, are more specific to cancer cells, potentially safer and more efficacious than the cytotoxic gents that target cell replication (Frampton 2013, Uzilov 2016, Tourneau 2015, Beaubier 2018).

To deliver personalized cancer targeted therapy, it is essential to use diagnostic tests that would accurately and comprehensively characterize the genomic alterations within individual tumors. Several technologies including Sanger sequencing (SGS, the gold standard), PCR, mass spectrometric genotyping, and other tests are currently used for the clinical assessment of a limited number of oncogenic markers. These tests may not perform parallel investigations of multiple targets and cannot address the increasing number and variety of therapeutically relevant gnomic alterations that occur in hundreds of cancer related genes with the amount of material obtained from biopsies (Frampton 2013, Rehm 2013, Arsenic 2015, Beaubier 2018).

Next generation sequencing (NGS), is becoming an attractive clinical diagnostic technology to detect most genomic alterations in the therapeutically relevant cancer genes in a single assay. NGS is not a test. but is an umbrella term for massively parallel DNA sequencing technology. The term NGS is used to emphasize the difference from the initial traditional gold standard single gene-based sequencing approaches that involve sequencing of one DNA strand at a time. NGS encompasses a variety of technologies that permit rapid parallel sequencing of millions of DNA segments, up to the entire genomes. These can perform three main levels of analysis: exome sequencing, genome sequencing, and disease targeted gene panels (Frampton 2013, Regier 2018).

A NGS cancer panel involves a complex 2-step process: 1. Wet bench process, which includes the handling of patient samples, extraction of nuclei acid, fragmentation and barcoding, target enrichment, adaptor ligation, library preparation, and generation of sequence reads. 2. Bioinformatics analysis of sequence data. This includes mapping sequence reads to the human reference genome, variant calling, annotation, and reviewing data in the right clinical context. Each of these steps require separate standards (Behjati 2013, Frampton 2013, McCourt 2013, Rehm 2013, American College of Medical Genetics and Genomics).

The number and scope of genes to be tested depend on the purpose of the test. A companion diagnostic test for standard care would require a limited number of genes, whereas NGS-based tests used for stratifying patients require the interrogation of a broader range of genes. Currently, there are several NGS platforms that perform sequencing of millions of small fragments of DNA in parallel. The platforms use different sequencing technologies, and due to the complexity and amount of sequencing data, and concerns about the reliability of the different NGS panels, several working groups (including the College of American Pathologists (CAP) and the American College of Medical Genetics and Genomics [ACMG]) have issued guidelines for NGS clinical testing. The assays or platforms should have a high-test sensitivity as cancer specimens may have a low percentage of tumor cells, i.e. high level of normal cell contamination. The test should also have a high specificity as a false positive result will have a negative impact on the choice of therapy (Frampton 2013, Kim 2017).

Cancer panel tests are mainly focused on actionable genomic alterations (variants) whose presence may help identify the most promising treatment approach. Different definitions of "actionable variants" have been used by researchers. While the majority defined it as the variant that can be targeted by a currently available drug (either FDA approved, off label use of an FDA approved drug, or a drug under investigation), others expanded the definition to include change in patient management on the prognostic implication or change in risk stratification. It is estimated that as many as one third of actionable changes in tumor analysis may be incorrectly classified as

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somatic changes. It is thus recommended to use matched tumor-normal DNA for genomic analysis to accurately identify and interpret actionable somatic and genetic changes that would have an important impact on the diagnosis and therapeutic management of cancer patients (Jones 2015, Kim 2017, Tan 2017, Regier 2018).

In recent years, several academic centers have adopted the use of NGS panels at the point of care to study cancer genomics and personalize patient care (precision oncology). However, the application of the NGS technology in the clinical context as a routine test to support the selection of therapy for cancer patients has its challenges. Most of cancer specimens are formalin-fixed paraffin embedded tissue (FFPE) which can degrade the DNA and RNA. This would require the application of robust nucleic acid extraction and sequencing library construction. In addition, many samples available for testing contain limited amount of tissue and in turn a limited amount of nucleic acid. The assays also need to be sensitive enough to detect gene alterations in specimens with a low tumor percentage. The use of the technology requires an infrastructure e.g. computer capacity and storage, as well as the application of rigorous statistical and analytical approaches to validate the accuracy of NGS technology for use in the clinical setting. An additional reported challenge is the personnel expertise required to comprehensively analyze and interpret the subsequent data, as well as skillfully extract and manage the clinically important information from the volume of data obtained. NGS has the potential to uncover a significant quantity of complex clinically and non-clinically actionable results with wide ranging implications for the patients and their families. Targeted therapies are limited by several factors including the availability, effectiveness and /or specificity of molecular inhibitor (targeted drug therapies) based on patients 'genetic information, heterogeneity the disease, resistance to a targeted therapy, and access to the treatment. It has also been reported that targeted therapies may be successful for some tumor types but not for others (Behjati 2013. Frampton 2013, Radovich 2016, Beaubier 2018).

FoundationOne CDx™ (F1CDx, Foundation Medicine, Inc.) a NGS test, was granted marketing approval by the US Food and Drug Administration (FDA) on November 30, 2017 to detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. The test can also identify which patients with non-small cell lung cancer (NSCLC), melanoma, breast cancer, colorectal cancer, or ovarian cancer may benefit from 15 different FDA-approved targeted treatment options (FDA website).

01/14/2019: MTAC Review

Evidence Conclusion:

- As indicated earlier in the report, it is difficult to set standards for assuring the analytical validity of NGS tests due to the amount and complexity of cancer genome sequencing and the different NGS technologies used. In general, however, the published validation studies suggest that NGS tests may have a high analytic validity, and lower clinical validity.
- There is insufficient evidence from published randomized clinical trials to determine that incorporating NGS into cancer care improves patient outcomes, such as treatment response and disease-free survival, or to support the use of molecularly targeted agents outside their indications based on tumor molecular profiling.
- More RCTs are needed to provide evidence on the utility of cancer genomics in clinical practice.

Articles: The literature search identified over 1,000 articles on NGS; the great majority of which were reviews, abstracts or articles not related to the current review. The search was filtered and narrowed down according the inclusion criteria based on PICO. Selected studies comparing the performance of NGS versus Sanger sequencing as well as randomized or nonrandomized studies evaluating the effectiveness and safety of applying the technology to cancer patients were included in the review. See Evidence Table

The use of Broad-Spectrum Tumor Molecular Profiling - Next Generation Sequencing (NGS) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Decipher Prostate Genomic Classifier

10/10/2022: MTAC Review

Evidence Conclusion:

Decipher genomic testing using biopsy specimen

- There is insufficient evidence for or against the analytical validity and clinical utility of Decipher test. Low quality evidence supports the clinical validity of Decipher test. Overall, the evidence is insufficient for or against the use of Decipher genomic testing using biopsy specimen.

Decipher genomic testing using radical prostatectomy specimen

- Analytical validity: There is a lack of studies.

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- Clinical validity: Low quality evidence from retrospective studies demonstrate that the Decipher Genomic Classifier is consistently superior in its prognostic and discriminatory ability in comparison to clinicopathologic variables for metastasis & prostate cancer-specific mortality.
- Clinical utility: Low quality evidence supports the clinical utility of Decipher testing. Decipher may influence treatment recommendations change in post prostatectomy patients with adverse pathologic characteristics.
- Overall, low quality evidence supports the use of Decipher genomic testing using radical prostatectomy specimens.

Articles: PubMed was searched through September 2022 with the search terms (Decipher OR genomic classifier OR 22-gene) AND (prostate). The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded several studies. See Evidence Table.

The use of Decipher Prostate Genomic Classifier does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

***Note:** Codes listed in the criteria above may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

Date Created	Date Reviewed	Date Last Revised
1997	10/04/2011[MDCRPC], 8/07/2012[MDCRPC], 11/06/2012[MDCRPC], 04/02/2013[MDCRPC], 05/07/2013[MDCRPC], 06/04/2013[MDCRPC], 08/06/2013[MPC], 03/04/2014[MPC], 06/03/2014[MPC], 07/01/2014[MPC], 10/07/2014[MPC], 11/04/2014[MPC], 02/03/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 06/05/2018[MPC], 06/04/2019[MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC],06/06/2023[MPC]	08/14/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description
05/11/2015	Array-Based Comparative Genomic Hybridization (aCGH): Removed MCG and reactivated GHC insufficient evidence criteria
06/02/2015	MPC approved MTAC recommendation of insufficient evidence for OVA1 & DecisionDx-Melanoma Testing
06/04/2015	Added Cologuard
06/30/2015	Added LCD link for cytogenetic studies
08/27/2015	Add LCD for CYP Genes
09/08/2015	Revised LCD CYP2C19 (CPT-81225), CYP2D6 (CPT-81226), CYP2C9(CPT81227), and VKORC1(CPT-81355) Genetic Testing (L36311), Cytogenetic Studies L34067
10/13/2015	Added Medicare molecular testing LCD
10/27/2015	Added codes that do not need review
11/18/2015	Added Medicare MolDX links
03/01/2016	Discontinue review for Factor II & V
08/30/2016	Combined Risk Prognosticator Test to Genetic Screening criteria
09/06/2016	Added Prostate Cancer Gene Expression Testing- Oncotype DX MCG A-0712 to criteria

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10/24/2016	Changed Veristrat to match Pharmacogenomic policy
11/01/2016	MPC approved to accept the genetic testing recommendations from the MCG 20th edition as outlined
01/23/2017	Added LCD 36544 & LCD 36186
04/04/2017	Added MTAC Review
05/16/2017	Added Percepta LCD
08/28/2017	Added ThyGeNEXT Oncogene Panel
09/18/2017	HFE gene – review no longer required CPT 81256
10/03/2017	Adopted MCG 21st ed. guidelines: A-0910, A-0909, A-0916, A-0907, A-0904, A-0908, A-0918, A-0926
10/11/2017	Removed MCG A-0917
12/05/2017	Adopted clinical criteria for Cystic Fibrosis testing
02/06/2018	MPC approved to adopt criteria for Decision Dx- Choroidal/Uveal Melanoma
03/26/2018	Added Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer
04/25/2018	Added language to BRAF testing
05/03/2018	Updated name changes with the MCG 22nd Edition
06/05/2018	MPC approved to adopt MCG* A-0823 and MCG* A-0957
08/07/2018	Added MTAC review from 7/9/18 for Microarray and Whole Exome for DD/ID
08/29/2018	Move code 81301 to no review at this time.
10/02/2018	Updated Micro Array for Evaluation of Intellectual Disability criteria
12/04/2018	MPC approved to adopt MCG* A-0598 Diabetes Mellitus (Maturity-Onset Diabetes of the Young)
01/08/2019	MPC approved to adopt criteria for Whole Exome Sequencing
02/05/2019	MPC approved to adopt policy of no coverage for Next Generation Sequencing (NGS) - Broad Spectrum Tumor Molecular profiling; added 01/2019 MTAC review
02/26/2019	Mammaprint: Send all cases to MD for review until criteria has been developed
04/02/2019	MPC approved to adopt criteria for Mammaprint
12/03/2019	MPC approved a non-coverage policy for Donor-derived cell-free DNA testing (e.g., Allosure)
04/07/2020	MPC approved non-coverage policy for 81540 CancerTYPE ID
04/29/2020	Removed code 81528
06/02/2020	Added section: “Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees.”. Requires 60-day notice, effective date 10/01/2020. Moved CPT codes 81402, 81403 and 81270 under Applicable Codes section that do not need review.
06/23/2020	Added CPT codes 81277, 81307, 81308, 81309, 81522, 81542, 81552, 875630087U, 0080U, 0081U, 0088U, 0089U, 0090U, 0091U, 0092U, 0105U, 0106U, 0107U, 0108U, 0109U, 0110U, 0111U, 0112U, 0113U, 0114U, 0115U, 0116U, 0117U, 0118U, 0119U, 0120U, 0121U, 0122U, 0123U, 0124U, 0125U, 0126U, 0127U, 0128U, 0129U, 0130U, 0131U, 0132U, 0133U, 0134U, 0135U, 0136U, 0137U, 0138U
07/22/2020	Removed CPT codes that do not require review: 81220, 81221, 81240, 81241, 81261, 81340, 81341, 81342, 81372, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81402, 81403, 81270.
10/06/2020	MPC approved to adopt MCG 24th ed. guidelines for the following: Narcolepsy - HLA Testing: A-1005, Transthyretin Amyloidosis - TTR Gene: A-1010, Retinal Dystrophy - RPE65 Gene: A-1011, Breast Cancer- PALB2: A-0989, Alpha-1 Antitrypsin Deficiency - SERPINA1 Gene: KP-1006, Paraganglioma-Pheochromocytoma (Hereditary) - Gene Testing and Gene Panel: A-0798; added exception for NGS for Advanced Cancer (CellNetix lab) to Invitae as preferred lab section. Removed codes section; will defer to pre-authorization code check tool.
05/04/2021	Updated Medicare LCD links, MCG Guideline information, and applicable codes. MPC approved to adopt MCG 25th edition guidelines for the following: Malignant Melanoma (Cutaneous) – BAP1, CDK4, and CDKN2A; Malignant Melanoma (Cutaneous) – BRAF V600 Testing; Renal Cancer (Hereditary) – Gene Panel; and Noonan Syndrome – Gene and Gene Panel Testing. Requires 60-day notice, effective date 10/1/2021.
08/03/2021	Updated Nephrology section, referencing separate criteria for Donor-derived cell-free DNA testing for Kidney Transplant Rejection (e.g., AlloSure).

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11/02/2021	MPC approved to expand coverage for Spinal Muscular Atrophy (SMA) Carrier Testing. Requires 60-day notice, effective date 04/01/2022.
12/07/2021	MPC approved to adopt expansion of coverage for Chromosomal Microarray testing to members who are undergoing invasive prenatal genetic testing (i.e., amniocentesis). Requires 60-day notice, effective date 05/01/2022.
12/07/2021	MPC approved to adopt a policy of non-coverage for the ConfirmMDx and SelectMDx genetic tests for prostate cancer. Requires 60-day notice, effective date 05/01/2022.
04/05/2022	MPC approved to adopt MCG* A-0782 with new indications in the 26th edition. Gene/gene panel testing for hereditary ovarian cancer criteria are in the process of being updated and will all be reviewed by the Medical Director on a case-by-case basis until finalized.
06/07/2022	MPC approved to adopt MTAC's recommendation of non-coverage and to continue the existing policy of insufficient evidence.
08/16/2022	MCG* A-0822 and A-0847 were deleted from the 26th edition guidelines; deleted from criteria
09/22/2022	Added Oncoplex (University of Washington) and Caris Life Sciences as preferred lab vendors for NGS
311/01/2022	Updated criteria for Chromosomal Microarray Testing to remain compliant with revisions to the WAC; also updated other related prenatal genetic testing that were mandated to no longer require medical review. Effective immediately to comply with WAC 246-680-010. 60-day notice required.
11/01/2022	MPC approved to adopt criteria for Thyroid Nodule Gene Expression Testing (ThyraMIR/ThyGeNEXT CPT 0245u+0018U), Prostate Cancer Gene Expression Testing (Prolaris 81541) and Prostate Cancer (ConfirmMDx CPT 81551). Requires 60-day notice, effective date 04/01/2023.
11/14/2022	Added the July 2022 MTAC reviews for ConfirmMDx and Prolaris for Prostate Cancer. Replaced SelectMDx temporary CPT code 81479 with new CPT code 0339U, effective 10/1/22.
12/06/2022	MPC approved to remove NRAS genetic test from this page as it is currently on pharmacogenomic page. MPC approved to remove BRAF testing from genetic screening page and move to Pharmacogenomic page. Effective immediately.
12/12/2022	Added ClonoSEQ 81479 to flag for medical director review.
01/03/2023	Clarified language on ClonoSEQ indications. Added Medicare LCD L38816 and LCA A58997.
01/18/2023	Added the MTAC review for Decipher Prostate Genomic Classifier.
01/25/2023	For Prolaris-clarified use in setting of radical prostatectomy.
04/03/2023	Updated Medicare links and applicable code 0340U for Medicare LCD L38816.
04/24/2023	Added Quest-QNatal as a preferred vendor for Cell Free Fetal DNA testing.
08/14/2023	Updated applicable MCG 27th edition guidelines with updated name changes and guidelines that were marked as deleted to *"There is insufficient evidence in the published medical literature to show clinical utility."* Please refer to the MCG 27th edition summary of changes for more detail.

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