Genomic micro-array and whole exome sequencing

Draft evidence report: public comment and response

December 18, 2017
Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC 27709

Lead Investigator:
Nedra Whitehead, PhD

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.
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Public Comments Submitted

The State of Washington’s Health Technology Assessment Program posted the draft health technology assessment (HTA) on the topic of “Genomic microarray and whole exome sequencing” for public comment between November 7, 2017 and December 7, 2017. Table 1 lists the comments received and submitting individual/organization.

**Table 1. Comments Received on Draft Evidence Report on “Genomic microarray and whole exome sequencing”**

<table>
<thead>
<tr>
<th>Number</th>
<th>Name and Title</th>
<th>Organization</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jessie Conta, MS, LCGC Genetic Counselor Supervisor</td>
<td>On behalf of: Department of Laboratories Seattle Children’s Hospital PLUGS (Patient-centered Laboratory Utilization Guidance Services)</td>
<td>Seattle, Washington</td>
</tr>
<tr>
<td>2</td>
<td>Katie Stoll, MS, LGC Director of Clinical Services</td>
<td>Genetic Support Foundation</td>
<td>Olympia, Washington</td>
</tr>
<tr>
<td>3</td>
<td>Kiana Siefkas Licensed and Certified Genetic Counselor</td>
<td>Prenatal Diagnosis and Treatment Program Seattle Children’s Hospital</td>
<td>Seattle, Washington</td>
</tr>
<tr>
<td>4</td>
<td>Jaeliah Thalberg, MS, MA Licensed and Certified Genetic Counselor</td>
<td>Legacy Medical Group</td>
<td>Vancouver, Washington</td>
</tr>
<tr>
<td>5</td>
<td>Debra Lochner Doyle, MS, LCGC State Genetics Coordinator</td>
<td>Screening &amp; Genetics Unit Washington State Department of Health</td>
<td>Kent, WA</td>
</tr>
</tbody>
</table>

Summary of Main Themes from Comments

1. All five commenters pointed out that whole exome sequencing is primarily designed and used to diagnosis single gene disorders and not chromosomal abnormalities and called for a separate technology assessment of WES for the purpose of diagnosing single gene disorders.

2. Four of five commenters stated that WES was not appropriate for the detection of chromosomal abnormalities and that it would be inappropriate to make coverage decisions for WES based on this HTA. Three commenters mentioned the need to include this limitation in the Executive Summary.

3. One comment regretted that the report did not consider the use of CMA in prenatal diagnosis.
Detailed Comments and Response

Comment 1

Feedback on Draft Evidence Report: Genomic micro-array and whole exome sequencing
From the Seattle Children’s Hospital Department of Laboratories Leadership and
Patient-centered Laboratory Utilization Guidance Services (PLUGS™)

As stated in the Genomic micro-array and whole exome sequencing Draft Evidence Report, the report
intended, “to help the Washington HCA make well-informed coverage determinations and thereby
improve the quality of health care services.” The report states as its purpose, “to review the safety,
efficacy, and cost of chromosomal microarrays (CMA) and whole exome sequencing (WES) when used
for the diagnosis and management of children with developmental and intellectual disabilities, autism
spectrum disorder, or multiple congenital anomalies.”

We have reviewed the Draft Evidence Report in its entirety and have the following feedback that we
hope you will strongly consider before using the report to develop policy.

Summary: The scope of the review, to include analysis of both CMA and WES in one summary report
raises concerns, due to the distinct differences between these two diagnostic tests. The technology is
currently not interchangeable. The statement that the “review was limited to the use of WES to detect
chromosomal abnormalities” (Limitations of this HTA, page 16) demonstrates a clear knowledge gap of
the reviewers. WES is not the appropriate technology to use to detect chromosomal abnormalities, so
is not surprising that the reviewers found a paucity of evidence deemed admissible to evaluate WES in
the clinical context.

The scope of this review is misleading, particularly if individuals limit their review to the Executive
Summary, which does not make it clear that the review is limited to the use of WES to detect
chromosomal abnormalities and that use of WES to identify mutations within single genes is excluded
from the assessment. This information is only available within the Background (page 6 “this HTA will
also not address...the use of WES to identify mutations within single genes” and page 26 “scope to keep
the HTA focused on CMA and WES testing for the diagnosis of chromosomal abnormalities.”)

The coverage policies from United Healthcare, Blue Cross Premera and Cigna are related to the use of
WES to identify mutations within single genes. It would be incorrect for plans to use the HTA review as
evidence in an assessment of policy related to WES. We know of at least one national payer who utilized
this review inappropriately when considering their own policy related to the use of WES to identify
mutations within single genes, rather than the intended scope of the current HTA (e.g., WES to detect
chromosomal abnormalities).

We have great concern about the broad impact of this HTA review in its current state. We strongly
recommend that the reports be separated into two distinct reviews, one for CMA and one for WES.
Further, the WES review should focus on the intended use of the test (sequence analysis to identify
mutations within single genes) to provide clear review of evidence to guide creation of rational
coverage policies.
Specific Feedback: We identified a number of errors within the review that warrant correction.

1. Table I. CPT Descriptions (page 20): CPT description listed for code 81415 is incorrect. The description should read: **Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequencing analysis.** Further, both 81415 and 81416 describe exome sequence analysis, which would be out of scope of this HTA, which is described as including, “review wa limited to the use of WES to detect chromosomal abnormalities.”

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<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81228</td>
<td>Cyto genetic constitutional (genome-wide) microarray analysis: interrogation of genomic regions for copy number variants (e.g., bacterial artificial chromosome (BAC) or oligo-based comparative genomic hybridization (CGH) microarray analysis)</td>
</tr>
<tr>
<td>81229</td>
<td>Cyto genetic constitutional (genome-wide) microarray analysis. Interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities.</td>
</tr>
<tr>
<td>81415</td>
<td>Cyto genetic constitutional (genome-wide) microarray analysis: interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities.</td>
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<tr>
<td>81416</td>
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2. Figure ES-1 contains a clear typographical error: “GMA” instead of “CMA”

3. Error in Table 1. Payer coverage for CMA and WES Testing (Page 24): Blue Cross (Premera) covers WES for specific conditions (table incorrectly specifies no coverage, but coverage is clearly outlined in the following text on page 24 and represented correctly in Table ES-2)

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<tr>
<th>Payer</th>
<th>CMA Testing</th>
<th>WES Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue Cross (Premera)</td>
<td>Covered for specific indications</td>
<td>Not covered</td>
</tr>
<tr>
<td>Kaiser Permanente</td>
<td>Covered for specific indications</td>
<td>Not covered</td>
</tr>
<tr>
<td>Cigna</td>
<td>Covered for specific indications</td>
<td>Covered for specific indications</td>
</tr>
<tr>
<td>Aetna</td>
<td>Covered for specific indications</td>
<td>Covered for specific indications</td>
</tr>
<tr>
<td>Humana</td>
<td>Covered for specific indications</td>
<td>Not covered</td>
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<td>Medicare</td>
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<tr>
<td>Tricare</td>
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<td>United Healthcare</td>
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</table>
Thank you for your consideration. Please contact us if you have additional questions, (206) 987-3353.

Signed by leadership within Seattle Children’s Hospital Department of Laboratories and Patient-centered Laboratory Utilization Guidance Services (PLUGS*)

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Project Manager – Communications & Outreach, PLUGS* (Patient-centered Laboratory Utilization Guidance Services)
Comment 1 Response

We agree that chromosomal microarray (CMA) and whole exome sequencing (WES) are not interchangeable, and CMA is used for detection of chromosomal abnormalities and copy number variants, while WES is primarily used for the detection of mutations in single genes. However, peer-reviewed studies have shown that, with appropriate bioinformatics protocols, WES can detect copy number variants with sensitivity comparable to medium resolution CMA. The scope of this HTA was defined early to be limited to the detection of chromosomal abnormalities and practical constraints limited the ability to expand the scope to also include single gene disorders. We have clarified the use of WES in the final evidence report and noted the limitation with respect to the exclusion of WES testing for single gene disorders. We concur with the comments that a separate report focused solely on WES, including its use for the diagnosis of single gene disorders, would be valuable.

We have corrected the errors noted by the commenters in points 2 and 3; point 1 is being evaluated by the Washington Health Technology Assessment program.
Comment 2

The main issues raised here are similar to Comment 1 so please see our response to comment 1.

Feedback on Draft Evidence Report: Genomic microarray and whole exome sequencing

From Genetic Support Foundation

We have reviewed the Genomic Microarray and Whole Exome Sequencing Draft Evidence Report and have the following feedback that we hope you will strongly consider.

The scope of the review, to include analysis of both CMA and WES in one summary report raises concerns, due to the distinct differences between these two diagnostic tests. The technology is currently not interchangeable. The statement that the “review was limited to the use of WES to detect chromosomal abnormalities” (Limitations of this HTA, page 16) demonstrates a clear knowledge gap of the reviewers. WES is not the appropriate technology to use to detect chromosomal abnormalities, so it is not surprising that the reviewers found a paucity of evidence deemed admissible to evaluate WES in the clinical context.

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We have great concern about the broad impact of this HTA review in its current state. We strongly recommend that the reports be separated into two distinct reviews, one for CMA and one for WES. Further, the WES review should focus on the intended use of the test (sequence analysis to identify mutations within single genes) to provide clear review of evidence to guide creation of rational coverage policies.

Please contact us if you have additional questions. T: 844.743.6384.

Thank you for your consideration.

Katie Stoll, MS LGC         Julie Simon, MS LGC

Comment 2 Response

The main issues raised here are similar to Comment 1 so please see our response to comment 1.
Comment 3


As stated in the Genomic micro-array and whole exome sequencing Draft Evidence Report, the report is intended, “to help the Washington HCA make well-informed coverage determinations and thereby improve the quality of health care services.” The report states as its purpose, “to review the safety, efficacy, and cost of chromosomal microarrays (CMA) and whole exome sequencing (WES) when used for the diagnosis and management of children with developmental and intellectual disabilities, autism spectrum disorder, or multiple congenital anomalies.”

We have reviewed the Draft Evidence Report in its entirety and have the following feedback that we hope you will strongly consider before using the report to develop policy.

Summary: The scope of the review, to include analysis of both CMA and WES in one summary report raises concerns, due to the distinct differences between these two diagnostic tests. The technology is currently not interchangeable. Chromosomal microarray is a test that can tell if small pieces of chromosomes are deleted or duplicated. This has implications for patients, as a chromosomal disorder often requires complex medical management. Whole exome sequencing looks for variation in the 20,000 known genes to find a single gene disorder that has caused the medical problems for the individual. We do this test, as it is a cost effective way to test multiple genes at the same time, which is necessary for many persons with features that fit several different genetic conditions. A diagnosis can guide medical management. Doing individual sequencing of each gene would be cost prohibitive.

Chromosomal microarray cannot detect single gene disorders. Whole exome sequencing cannot detect chromosomal disorders. The statement that the “review was limited to the use of WES to detect chromosomal abnormalities” (Limitations of this HTA, page 16) demonstrates a clear knowledge gap of the reviewers. WES is not the appropriate technology to use to detect chromosomal abnormalities, so it is not surprising that the reviewers found a paucity of evidence deemed admissible to evaluate WES in the clinical context.

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The coverage policies from United Healthcare, Blue Cross Premera and Cigna are related to the use of WES to identify mutations within single genes. It would be incorrect for plans to use the HTA review as evidence in an assessment of policy related to WES. We know of at least one national payer who utilized this review inappropriately when considering their own policy related to the use of WES to identify mutations within single genes, rather than the intended scope of the current HTA (e.g., WES to detect chromosomal abnormalities).

We have great concern about the broad impact of this HTA review in its current state. We strongly recommend that the reports be separated into two distinct reviews, one for CMA and one for WES. Further, the WES review should focus on the intended use of the test (sequence analysis to identify mutations within single genes) to provide clear review of evidence to guide creation of rational coverage policies.

Comment 3 Response

The main issues raised here are similar to Comment 1 so please see our response to comment 1.
Comment 4

From: Thalberg, Jaellah S :LMG Legacy Medical Group  [mailto:JTHALBER@LHS.ORG]
Sent: Thursday, December 7, 2017 4:08 PM
To: HCA ST Health Tech Assessment Prog <SHTAP@HCA.WA.GOV>
Subject: microarray and WES

Feedback:

- Whole exome sequencing and array are two very complex and very different technologies. It is not appropriate to lump these two testing strategies together in a review.
- The statement “review was limited to use of WES to detect chromosome abnormalities”. WES is NOT designed to screen for chromosome aneuploidies nor should be used for that purpose. Clearly the reviewers do not understand the purpose of WES and why there was so limited evidence to assess for these changes.
- The fact that using WES for single gene disorders was excluded is confusing since this is what WES is designed for.
- CMA should be recommended as a first line test as it assesses for many more conditions compared to karyotyping for almost the same cost.
- Knowing a diagnosis in the family paves the way for prenatal diagnosis in future pregnancies as well as recurrence risk-not to mention management and treatment changes.
- The report acknowledges that all genetic professional societies endorse CMA as a first line test yet fails to take this into consideration when making their recommendations. I would think the experts have a pretty good handle on appropriate test ordering.
- I am concerned the report excludes prenatal diagnosis and these technologies since many organizations use these recommendations to approve or deny coverage of testing in general and generally don’t parse out certain populations or circumstances or timing in one’s life when it could be useful

Jaellah S. Thalberg, MS, MA
Licensed and Certified Genetic Counselor
Legacy Medical Group-Maternal Fetal Medicine
503-413-1122 (p) 503-413-2829 (f)

Comment 4 Response

The main issues raised here are similar to Comment 1 so please see our response to comment 1. Recommendations regarding the appropriate use or coverage of testing are not within the scope of the health technology assessment. The population for this HTA was focused on children. We agree with that a synthesis of testing in the prenatal context would be valuable but was not possible to include within this HTA for practical reasons.
Comment 5

From: Doyle, Debra (DOH)  
Sent: Friday, December 8, 2017 4:05 PM  
To: HCA ST Health Tech Assessment Prog <SHTAP@HCA.WA.GOV>  
Subject: Comments regarding CMA and WES Assessment

Dear Sirs;

I am writing to provide my comments concerning the Genomic Microarray and whole exome sequencing DRAFT evidence report currently open for public comment.

I appreciate the work that goes into such assessments, however, my comments will reflect only my concerns. In the background condition description, chromosomal abnormalities are described. Yet the purpose statement states that the review is evaluating these two testing strategies as they relate to the “diagnosis and management of children with intellectual disabilities, autism spectrum disorder or, multiple congenital anomalies.” These conditions can be chromosomal but can also be related to specific mutations within a gene. The selection of which test, CMA, WES or both is important and therefore it is important that within this assessment the reader understands that CMA is looking for chromosomal error while WES is looking for gene specific mutations. The latter is not at all described. This begs the question, were the authors clear on what they were looking for within their literature review? Furthermore, the disease burden describes common chromosomal aneuploids but fails to describe the disease burden of intellectual disabilities, autism spectrum disorder or multiple congenital anomalies.

I am also slightly confused by the statement and page #3 - However, the circumstances in which these tests are most useful and their contribution to the medical and educational management and ultimate health outcomes of affected children are unclear. The authors just stated that these tests had higher diagnostic yield and that management in over half the children identified. Even if the strength of evidence is low or very low (potentially due to the fact that fortunately most children do not have these conditions and this technology is relatively new so there are fewer studies published) it would appear the data reported here suggest these circumstances are appropriate for these testing strategies and that the medical management can best be tailored for the child and family because of the results.

I thank you for the opportunity to review this work.

Be well,

Debra Lochner Doyle, MS, LCGC  
State Genetics Coordinator  
Washington State Department of Health  
Screening & Genetics Unit  
20425 72nd Ave. S. Suite #310  
Kent, WA 98032

PH: 253-395-6742  
Fax: 253-3956737

Comment 5 Response

The main issues raised here are similar to Comment 1 so please see our response to comment 1. We have added information regarding the disease burden of intellectual and development disabilities, congenital anomalies and autism to the report.
Feedback on Draft Evidence Report: Genomic micro-array and whole exome sequencing
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**Summary:** The scope of the review, to include analysis of both CMA and WES in one summary report raises concerns, due to the distinct differences between these two diagnostic tests. The technology is currently not interchangeable. Chromosomal microarray is a test that can tell if small pieces of chromosomes are deleted or duplicated. This has implications for patients, as a chromosomal disorder often requires complex medical management. Whole exome sequencing looks for variation in the 20,000 known genes to find a single gene disorder that has caused the medical problems for the individual. We do this test, as it is a cost effective way to test multiple genes at the same time, which is necessary for many persons with features that fit several different genetic conditions. A diagnosis can guide medical management. Doing individual sequencing of each gene would be cost prohibitive.

**Chromosomal microarray cannot detect single gene disorders. Whole exome sequencing cannot detect chromosomal disorders.** The statement that the “review was limited to the use of WES to detect chromosomal abnormalities” (Limitations of this HTA, page 16) demonstrates a clear knowledge gap of the reviewers. WES is not the appropriate technology to use to detect chromosomal abnormalities, so it is not surprising that the reviewers found a paucity of evidence deemed admissible to evaluate WES in the clinical context.

The scope of this review is misleading, particularly if individuals limit their review to the Executive Summary, which does not make it clear that the review is limited to the use of WES to detect chromosomal abnormalities and that use of WES to identify mutations within single genes is excluded from the assessment. This information is only available within the Background (page 6 “this HTA will also not address...the use of WES to identify mutations within single genes” and page 26 “scope to keep the HTA focused on CMA and WES testing for the diagnosis of chromosomal abnormalities.”)

The coverage policies from United Healthcare, Blue Cross Premera and Cigna are related to the use of WES to identify mutations within single genes. It would be incorrect for plans to use the HTA review as evidence in an assessment of policy related to WES. We know of at least one national payer who utilized this review inappropriately when considering their own policy related to the use of WES to identify mutations within single genes, rather than the intended scope of the current HTA (e.g., WES to detect chromosomal abnormalities).

We have great concern about the broad impact of this HTA review in its current state. We strongly recommend that the reports be separated into two distinct reviews, one for CMA and one for WES. Further, the WES review should focus on the intended use of the test (sequence analysis to identify mutations within single genes) to provide clear review of evidence to guide creation of rational coverage policies.
Thank you for your consideration. Please contact us if you have additional questions, (206) 987-7973.

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Feedback:

- Whole exome sequencing and array are two very complex and very different technologies. It is not appropriate to lump these two testing strategies together in a review.
- The statement “review was limited to use of WES to detect chromosome abnormalities”. WES is NOT designed to screen for chromosome aneuploidies nor should be used for that purpose. Clearly the reviewers do not understand the purpose of WES and why there was so limited evidence to assess for these changes.
- The fact that using WES for single gene disorders was excluded is confusing since this is what WES is designed for.
- CMA should be recommended as a first line test as it assesses for many more conditions compared to karyotyping for almost the same cost.
- Knowing a diagnosis in the family paves the way for prenatal diagnosis in future pregnancies as well as recurrence risk—not to mention management and treatment changes.
- The report acknowledges that all genetic professional societies endorse CMA as a first line test yet fails to take this into consideration when making their recommendations. I would think the experts have a pretty good handle on appropriate test ordering.
- I am concerned the report excludes prenatal diagnosis and these technologies since many organizations use these recommendations to approve or deny coverage of testing in general and generally don’t parse out certain populations or circumstances or timing in one’s life when it could be useful.

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Dear Sirs;

I am writing to provide my comments concerning the Genomic Microarray and whole exome sequencing DRAFT evidence report currently open for public comment.

I appreciate the work that goes into such assessments, however, my comments will reflect only my concerns. In the background condition description, chromosomal abnormalities are described. Yet the purpose statement states that the review is evaluating these two testing strategies as they relate to the “diagnosis and management of children with intellectual disabilities, autism spectrum disorder or, multiple congenital anomalies.” These conditions can be chromosomal but can also be related to specific mutations within a gene. The selection of which test, CMA, WES or both is important and therefore it is important that within this assessment the reader understands that CMA is looking for chromosomal error while WES is looking for gene specific mutations. The latter is not at all described. This begs the question, were the authors clear on what they were looking for within their literature review? Furthermore, the disease burden describes common chromosomal aneuploids but fails to describe the disease burden of intellectual disabilities, autism spectrum disorder or multiple congenital anomalies.

I am also slightly confused by the statement and page #3 - However, the circumstances in which these tests are most useful and their contribution to the medical and educational management and ultimate health outcomes of affected children are unclear. The authors just stated that these tests had higher diagnostic yield and that management in over half the children identified. Even if the strength of evidence is low or very low (potentially due to the fact that fortunately most children do not have these conditions and this technology is relatively new so there are fewer studies published) it would appear the data reported here suggest these circumstances are appropriate for these testing strategies and that the medical management can best be tailored for the child and family because of the results.

I thank you for the opportunity to review this work.

Be well,

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