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Private payer coverage policies for exome sequencing (ES) in pediatric patients: trends over time and analysis of evidence cited

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Purpose: Exome sequencing (ES) is being adopted for neurodevelopmental disorders in pediatric patients. However, little is known about current coverage policies or the evidence cited supporting these policies. Our study is the first in-depth review of private payer ES coverage policies for pediatric patients with neurodevelopmental disorders.

Methods: We reviewed private payer coverage policies and examined evidence cited in the policies of the 15 largest payers in 2017, and trends in coverage policies and evidence cited (2015–2017) for the five largest payers.

Results: There were four relevant policies ($N = 5$ payers) in 2015 and 13 policies ($N = 15$ payers) in 2017. In 2015, no payer covered ES, but by 2017, three payers from the original registry payers did. In 2017, 8 of the 15 payers covered ES. We found variations in the number and types of evidence cited. Positive coverage policies tended to include a larger number and range of citations.

Conclusion: We conclude that more systematic assessment of evidence cited in coverage policies can provide a greater understanding of coverage policies and how evidence is used. Such assessments could facilitate the ability of researchers to provide the needed evidence, and the ability of clinicians to provide the most appropriate testing for patients.

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Keywords: exome sequencing; Payer coverage policies; Pediatrics; Neurodevelopmental delay

INTRODUCTION

Next-generation sequencing has changed the model of clinical genetic testing[1,2] as it allows the interrogation of distinct groups of genes (gene panels), the exome, or the genome to achieve a genetic diagnosis. Exome sequencing (ES) enables parallel interrogation of many genes for the diagnosis of more complex genetic conditions with high locus heterogeneity (for example, intellectual disability or autism). ES may result in higher diagnostic yield, shorter time to diagnosis, and improved cost-efficiency compared with standard care.[3,4] Accordingly, ES is emerging as a first-line genetic test for the evaluation of some neurodevelopmental disorders in pediatric patients.[5] ES generates a lot of information, but assessments as to its clinical utility (CU) are context specific[6] and complicated by uncertainty in variant interpretation.

Payer coverage for ES can impact whether patients are tested, how they are tested, and ultimately their clinical outcome.[7,8] A previous payer coverage study reviewed 2015 coverage policies from the largest five payers for multigene tests and found no coverage for ES. The study also did not explore the evidence cited in support of coverage policies.[7] Payers cite a variety of types of evidence in their coverage policies. Thus it is important to understand the number and types of evidence cited in coverage policies to assess the role of evidence on coverage policies.

The objective of this study was to review private payer coverage policies for ES in pediatric populations with neurodevelopmental delays to examine trends in coverage policies and evidence cited in policies from 2015 to 2017. This study augments the body of literature by providing the current status of ES coverage of 153 million lives (about 50% of the US population), a historical perspective of coverage from 2015 to 2017, and an overview of evidence cited by payers when developing coverage policies. Results of this study are important to better understand the variability across existing coverage policies and facilitate a more transparent and systematic assessment of the evidence used by payers to determine CU and resultant coverage policies.

MATERIALS AND METHODS

Data sources and collection

We used data pertaining to ES in 2015 for policies from the largest five private payers from *The University of*

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California–San Francisco (UCSF) Center for Translational and Policy Research (TRANSPERS) Payer Coverage Policy Registry. The Registry is described in Phillips et al.[7] and has been used in several payer coverage policy analyses.[7,9–11] We could not expand the Registry data to include policies from 2015 for additional payers, as these older policies are not available and most payers post only their current coverage policies on their websites.

Data pertaining to ES in 2017 were not in the Registry and therefore we obtained data on the largest 15 private payers for 2017 and their policies. We searched individual payers' medical policy websites to obtain policies pertaining to ES. We excluded one payer that does not publicly post their coverage policies (Kaiser Permanente). Data were independently coded by two authors (MD, SP) and discrepancies resolved by discussion.

Search strategy and policy selection

Based on the Registry's coded 2015 ES policies, we searched payers' websites for updated versions of those policies. We then identified additional ES policies by going onto the largest 15 payers' websites and searching for policies using the terms "Genetic Test," "Sequencing," and "Pediatrics" in each payer's medical policy search engine platform. Policy titles and text were individually screened to determine if they met criteria for inclusion in the database. We included policies that specifically addressed ES as a clinical diagnostic test and excluded policies that addressed single-gene testing or gene panel sequencing only, or did not include a provision on ES. We identified 13 publicly available, ES-relevant policies from the largest 15 payers (described in Supplementary Table 1).

We collected the references cited in each policy in support of their policy and each citation was reviewed for the technology evaluated (e.g., genome sequencing (GS)/ES), the population studied, diagnostic yield results, key conclusions, and the number of times cited across collected policies. Three types of studies were included: clinical studies, clinical guidelines, and health technology assessments (HTA). Only clinical studies that evaluated ES involving a pediatric population (0–17 years of age) were included. Clinical guidelines and health technology assessments were included if they were publicly available. We defined *clinical guidelines* as statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. We defined *health technology assessment* as a result of a multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.

Review of policies

First, we examined both 2015 and 2017 policies for stated ES coverage determinations (medically necessary or investigational/not medically necessary), and the clinical scenario(s) required to meet a medically necessary coverage policy (Supplementary Table 1). We then examined cited studies in each coverage policy to assess (1) the number of citations, (2) the type of study cited (clinical studies, health technology assessments, clinical guidelines, and expert interviews) using the category definitions in Chambers et al.[10] and (3) whether studies were supportive of clinical utility (CU) based on the conclusion statements within each citation (see Table 1). For item 3, we classified each citation's conclusion statements into three categories based on the study's support of CU as Favorable, Neutral, or Not Favorable (Supplementary Table 2). Favorable was defined as preponderance of conclusions that supported the use of ES (e.g., "our study supports the use of ES"); Neutral was defined as preponderance of conclusions that neither supported nor refuted the use of ES (e.g., "our study provides evidence that next-generation sequencing can have high success rates in a clinical setting, but also highlights key challenges"); Not Favorable was defined as preponderance of conclusions that stated evidence was insufficient to support use of ES (e.g., "exome sequencing is considered

Table 1 Citations referenced in policies: citation type and favorability

Citation	Citation type	Citation favorability[a]
Dixon-Salazar 2012	Clinical study	Favorable
ACMG 2012	Clinical guidelines	Favorable
Need 2012	Clinical study	Neutral
Yang 2013[3]	Clinical study	Favorable
BCBSA 2013	Technology assessment	Not favorable
Rehm 2013	Clinical guidelines	Other
Green 2013	Clinical guidelines	Other
Lee 2014	Clinical study	Favorable
Yang 2014	Clinical study	Favorable
Dewey 2014	Clinical study	Other
Iglesias 2014	Clinical study	Favorable
Soden 2014	Clinical study	Favorable
Srivastava 2014[14]	Clinical study	Favorable
Valencia 2015	Clinical study	Favorable
Farewell 2015	Clinical study	Favorable
Taylor 2015	Clinical study	Other
BCBSA 2015	Technology assessment	Not favorable
Beale 2015	Expert interview study	Other
Posey 2016	Clinical study	Other
Nolan 2016[13]	Clinical study	Favorable
Stark 2016[5]	Clinical study	Favorable
BCBSA 2016	Technology assessment	Favorable

[a]Details on favorability determination in Supplemental Appendix Table 2: Favorable was defined as preponderance of conclusions that supported the use of exome sequencing (ES) (e.g., "our study supports the use of ES"), Neutral was defined as preponderance of conclusions that neither supported nor refuted the use of ES (e.g., "our study provides evidence that next-generation sequencing can have high success rates in a clinical setting, but also highlights key challenges"); Not Favorable was defined as preponderance of conclusions that stated evidence was insufficient to support use of ES (e.g., "exome sequencing is considered investigational"); and Other was defined as studies that were not clinical studies, clinical guidelines, or health technology assessments that did not directly inform the use of ES (i.e. implementation guideline for returning findings or validation of ES, or clinical study on GS)

Table 2 2015 and 2017 payer coverage policies for ES

Payer	2015 Covered? (Policy Name)	2017 Covered? (Policy Name)
United Healthcare	**NO** (Genetic Testing)	**YES** (Genetic Testing)
HCSC	**NO** (Whole Exome and Whole Genome Sequencing for Diagnosis of Patients with Suspected Genetic Disorders)	**YES** (EviCORE: Molecular and Genetic Test-Specific Policies)
WellPoint Anthem BC	**NO** (Genetic Testing of an Individual's Genome for Inherited Diseases)	**NO** (Genetic Testing of an Individual's Genome for Inherited Diseases)
Aetna	**NO** (Genetic Testing)	**NO** (Genetic Testing)
Cigna	No Policy	**YES** (Whole Exome and Whole Genome Sequencing)
Highmark (BCBS)	Policy Not Available	**YES** (Whole Exome Sequencing)
Independence Blue Cross	Policy Not Available	**YES** (EviCORE: Molecular and Genetic Test-Specific Policies)
BCBS Michigan	Policy Not Available	**YES** (Genetic Testing - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders)
CareFirst (BCBS)	Policy Not Available	**YES** (Whole Exome and Genome Sequencing for Cancerous and Noncancerous Conditions)
Blue Shield of CA	Policy Not Available	**YES** (Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders)
Humana	Policy Not Available	**NO** (Whole Genome/Exome Sequencing and Genome-Wide Association Studies)
BCBS Tennessee	Policy Not Available	**NO** (Whole Exome and Genome Sequencing)
BCBS Alabama	Policy Not Available	**NO** (Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders)
Kaiser Permenante*	Policy Not Available	Policy Not Available
Health Net**	Policy Not Available	Policy Not Available

*Kaiser Permanente coverage policies are not publicly available
**Health Net has a coverage policy for Genetic Testing but it does not address ES

Table 3 Citation type and number of citations for evidence cited by payer in 2017 coverage policies for exome sequencing (ES)

	Payer	Blue Shield of CA	BCBS Michigan	BCBS Alabama	Independence Blue Cross	HCSC	Cigna	CareFirst (BCBS)	United Healthcare	BCBS Tennessee	WellPoint Anthem BC	Aetna	Humana	Highmark (BCBS)
Citation Type	**No. of Citations**	18	18	17	15	10	7	7	3	3	3	2	2	1
Clinical Study	Dixon-Salazar 2012	X	X	X	X	X								
	Need 2012									X				
	Yang 2013	X	X	X	X		X	X						
	Dewey 2014	X	X	X				X					X	
	Iglesias 2014	X	X	X	X	X		X						
	Lee 2014	X	X	X	X	X					X			
	Soden 2014	X	X	X	X									
	Srivastava 2014	X	X	X	X			X						
	Yang 2014	X	X	X	X	X					X		X	
	Farewell 2015	X	X	X	X	X	X							
	Taylor 2015	X	X	X					X					
	Valencia 2015	X	X	X	X	X								
	Nolan 2016	X	X	X	X	X								
	Posey 2016	X	X	X	X			X	X					
	Stark 2016	X	X	X	X	X								
Clinical Guidelines	ACMG 2012						X							X
	Green 2013	X	X	X	X	X	X		X		X			
	Rehm 2013	X	X	X	X	X	X							
Expert Interview Study	Beale 2015						X					X		
Technology Assessment	BCBSA 2013	X	X	X	X		X			X		X		
	BCBSA 2015							X		X				
	BCBSA 2016	X	X					X						

Dark shaded policies are no coverage policies

Table 4 Citation favorability in covered and not covered 2017 payer coverage policies for exome sequencing (ES)

		Policies Covering WES								Policies Not Covering WES				
Citation Favorability	**Citation**	Blue Shield of CA	BCBS Michigan	Independence Blue Cross	HCSC	Cigna	CareFirst (BCBS)	United Healthcare	Highmark (BCBS)	BCBS Alabama	BCBS Tennessee	WellPoint Anthem BC	Aetna	Humana
Favorable*	ACMG 2012					X			X					
	Dixon-Salazar 2012	X	X	X	X					X				
	Yang 2013	X	X	X		X	X			X				
	Yang 2014	X	X	X	X					X		X		X
	Iglesias 2014	X	X	X	X		X			X				
	Soden 2014	X	X	X						X				
	Srivastava 2014	X	X	X			X			X				
	Lee 2014	X	X	X	X					X		X		
	Valencia 2015	X	X	X	X					X				
	Farewell 2015	X	X	X	X	X				X				
	Nolan 2016	X	X	X	X					X				
	Stark 2016	X	X	X	X					X				
	BCBSA 2016	X	X				X							
Neutral**	Need 2012										X			
Not Favorable***	BCBSA 2013	X	X	X		X				X	X		X	
	BCBSA 2015						X				X			
Other****	Rehm 2013	X	X	X	X	X				X				
	Beale 2015					X							X	
	Green 2013	X	X	X	X	X		X		X		X		
	Dewey 2014	X	X				X			X				X
	Taylor 2015	X	X					X		X				
	Posey 2016	X	X	X			X	X		X				

Dark shaded policies are no coverage policies

*Favorable was defined as preponderance of conclusions that supported the use of ES (e.g., "our study supports the use of ES")

**Neutral was defined as preponderance of conclusions that neither supported nor refuted the use of ES (e.g., "our study provides evidence that next-generation sequencing can have high success rates in a clinical setting, but also highlights key challenges")

***Not Favorable was defined as preponderance of conclusions that stated evidence was insufficient to support use of ES (e.g., "exome sequencing is considered investigational")

****Other was defined as studies that were not clinical studies, clinical guidelines, or health technology assessments that did not directly inform the use of ES (i.e., implementation guideline for returning secondary findings or validation of ES, or clinical study on GS)

Table 5 Trends in citations by whether policies covered/did not cover exome sequencing (ES) in 2015 and 2017

Payer	United Healthcare		HCSC		Cigna		WellPoint Anthem BC		Aetna	
Year	2015	2017	2015	2017	2015	2017	2015	2017	2015	2017
Covered?	NO	YES	NO	YES	No Policy	YES	NO	NO	NO	NO
Citations	1	3	6	10	N/A	7	2	3	1	2
Dixon-Salazar 2012			X	X	N/A					
ACMG 2012					N/A	X				
Need 2012					N/A					
Yang 2013			X		N/A	X				
BCBSA 2013			X		N/A	X	X		X	X
Rehm 2013				X	N/A	X				
Green 2013		X	X	X	N/A	X	X	X		
Lee 2014				X	N/A			X		
Yang 2014				X	N/A			X		
Dewey 2014			X		N/A					
Iglesias 2014				X	N/A					
Soden 2014					N/A					
Srivastava 2014					N/A					
BCBSA 2014			X		N/A					
Valencia 2015				X	N/A					
Farewell 2015				X	N/A	X				
Taylor 2015		X			N/A					
BCBSA 2015					N/A					
Beale 2015					N/A	X				X
MCG Care Guidelines, WGS/WES 2015	X				N/A					
Posey 2016	N/A	X	N/A		N/A		N/A		N/A	
Nolan 2016	N/A		N/A	X	N/A		N/A		N/A	
Stark 2016	N/A		N/A	X	N/A		N/A		N/A	
BCBSA 2016	N/A		N/A		N/A		N/A		N/A	

Dark shaded policies are no coverage policies. N/A: Not Applicable

investigational"). A fourth category, called Other, was used for studies that were clinical studies, clinical guidelines, or health technology assessments that did not directly inform the use of ES (i.e., guidelines for returning findings or validation of ES, or clinical study on GS) (See Table 1). Conclusion statements and favorability coding justification are shown in Supplementary Table 2. Data were independently coded by two authors (MD, SP) and discrepancies resolved by discussion. We describe trends but we did not statistically assess differences.

RESULTS

Policies Included

We identified four relevant policies in 2015 ($N = 5$ payers) and 13 policies in 2017 ($N = 15$ payers) (See Table 2). These payers represent 160 million enrolled lives.

Coverage trends 2015–2017

In 2015, none of the largest five payers covered ES, but by 2017, three of the original registry payers covered ES. In the expanded 2017 sample of the 15 largest payers, 8 covered ES

(53% of 160 million enrolled lives) (see Table 2). All positive coverage policies included detailed clinical scenarios for coverage of ES and language regarding the diagnosis of suspected genetic origin and the need for medical management decisions to be impacted by that diagnosis (Supplemental Table 1). All negative coverage policies stated, "the clinical utility of ES has not been established and therefore not medically necessary."

Analysis of cited studies from coverage policies in largest 15 payers from 2017

We identified 22 citations used across multiple payers to inform coverage policy making in 2017 (see Table 3; Supplemental Reference List). All payers reviewed diverse reference categories (clinical studies, clinical guidelines, health technology assessments, or expert interviews) with publication dates between 2012 and 2016 (see Table 2).

We found wide variation in the number and types of citations in positive or negative coverage policies (Table 3). The number of citations varied from one clinical guideline from 2012 cited in a positive coverage policy (Highmark Blue Cross Blue Shield [BCBS]) to 17 citations of varying types that were cited in a negative coverage policy (BCBS Alabama). Of particular interest was that these same 17 citations, with the addition of one more, were then cited in two positive coverage policies (BS of California, BCBS Michigan). We found a trend in the number of citations included in payer policies. Based on Table 3, six of the eight positive coverage policies cited seven or more citations, while only one of the five noncoverage policies cited seven or more citations. Payers with negative coverage policies cited fewer and older references compared with positive coverage policies. We did not find a trend in the types of citations used in either positive or negative coverage policies.

Findings for the association of favorability of citations with coverage indicate a more consistent pattern (Table 4). Positive coverage policies tended to include a larger number and range of citations (favorable or unfavorable). Negative coverage policies tended to include only Neutral, Not Favorable, and Other citations. Interestingly, one payer cited 16 of the most widely referenced clinical studies, guidelines, or health technology assessments, many of which were favorable and cited in positive coverage policies, and yet arrived at a negative coverage policy (BCBS Alabama).

Comparison of cited studies in 2015 and 2017 policies for largest five payers

As noted above, three of the five largest payers changed their policies on ES coverage between the years 2015 and 2017, although with no identifiable or consistent pattern of studies that were added or removed by payers. The evidence cited by payers in 2017, as compared with 2015, included the addition of 3–8 studies (and removal of older studies) in four of the five payers (see Table 5). Specifically, one payer (HCSC) removed four citations and added eight citations when they moved from a negative to a positive coverage policy and another payer (United Healthcare) issued a positive coverage policy with the addition of three citations and removal of one citation. Lastly, the third payer (Cigna) added a new medical policy specific to ES, with seven citations and a positive coverage determination.

The medical policies that retained their negative coverage of ES were updated within this timeframe, albeit with fewer changes to citations. Payers who added two or fewer citations kept a negative coverage policy. For example, one payer (Anthem) added two studies and removed one from their policy, and the other payer (Aetna) added a single expert interview study.

DISCUSSION

In sum, we found a shift from no coverage among the largest five private payers in 2015 to over 50% coverage by the largest 15 payers in 2017 for the use of ES in pediatric patients with neurodevelopmental disorders. We found substantial variation in the number and types of citations used by payers in their coverage policies, with 1–18 citations being used in positive coverage policies and with one exception, three or fewer being used in negative coverage policies. We identified two trends: (1) policies with more than seven citations were typically positive coverage policies and those with fewer than five citations were typically negative coverage policies, and (2) positive coverage policies tended to include a larger number and range of citations (favorable or unfavorable).

Our study found a wide variety of types of citations (e.g., study type) used across payers in their coverage policies. Interestingly, no patterns could be distinguished between types of citations cited and payer coverage. Some payers renewed a noncoverage policy for ES in 2017 without adding new clinical evidence, while most payers updated their ES policies with citations of clinical evidence. However, we did not find consistent patterns relating to the type of evidence cited and positive or negative coverage of ES. We found two payers changed their coverage policies from noncovered to covered with the addition of clinical studies that had been previously published in 2015 or earlier.

It is possible that the variability we saw in the citations used in the coverage policies exist because payers use different criteria to identify, include, and evaluate new literature. Additional information or expert/nonexpert opinions (e.g., medical policy boards, advocacy groups) may be used to inform the payers' ES coverage policy decision-making process, and these are not discernible using the publicly available policy information.

We found that positive coverage policies tended to include a larger number and range of citations (favorable or unfavorable). Negative coverage policies tended to include only Neutral, Not Favorable, and Other citations. An example of a favorable citation is Stark et al., which concluded "singleton ES outperformed standard care in terms of diagnosis rate and the benefits of a diagnosis, namely, impact on management of the child and clarification of reproductive risks for the extended family in a timely manner."[5] An example of a not favorable

citation is the 2015 Blue Cross Blue Shield Association assessment that "ES is considered investigational."[12]

One challenge is that few studies have evaluated whether and to what extent ES results will affect medical outcomes or change treatment plans, rather than simply provide a diagnosis. For example, we note three recent studies in which the CU of ES was analyzed. These studies found that ES can result in lower long-term costs and more timely diagnosis,[13] a change in clinical management following exome diagnosis in 32.6% of diagnosed participants,[5] and a change in management for all patients with a presumptive diagnosis concluding that a high diagnostic yield of ES supports its use in pediatric practice and that earlier diagnosis may also impact medical management, prognostication, and family planning.[14]

Our results are similar to other studies that have found the CU evidence cited by payers to be reflected in their coverage policies. In 2010, Trosman et al. described the coverage policy development for the 21-gene, OncoTypeDx in which payers reported clinical evidence as the most important factor in decision making, but all used some health-care system factors (e.g., physician adoption or medical society endorsement) to inform decision making. They concluded policy variation may emerge from the range of factors used and perception of the evidence.[15] Similarly, the use of health technology assessment played a key role in the development of coverage policies for personalized medicine.[16] Furthermore, this variability of types of citations is similarly described by Chambers, who compared multigene panels and sequencing tests with other types of medical interventions, and found payers cited clinical studies and other evidence types less often in their coverage policies for multigene panels than they did in their coverage policies for other types of medical interventions.[10] Similarly, the trend of citing limited CU evidence to support some coverage policies is similar to trends seen regarding other multigene tests. For example, Dervan found that payers utilized the standard evidentiary framework (analytic validity/clinical validity/clinical utility) when evaluating cell-free DNA (cfDNA) screening, but varied in their interpretation of the sufficiency of the evidence. Professional guidelines, large clinical validity studies, and decision analytic models regarding health outcomes appeared highly influential in coverage decisions.[9]

More recently, our previous study identified challenges for coverage policy development in tumor sequencing that suggest the challenges that payers perceive in coverage policies for multigene tests, which may also impact ES coverage policies.[8] Trosman et al. found all interviewed payers saw potential for next-generation tumor sequencing (NGTS) benefits, but all noted challenges to formal coverage: 80% stated that inherent features of NGTS do not fit the medical necessity definition required for coverage, 70% viewed NGTS as a bundle of targets versus comprehensive tumor characterization and may evaluate each target individually, and 70% expressed skepticism regarding new evidence methods proposed for NGTS. Fifty percent of payers expressed sufficient concerns about NGTS adoption and implementation that precluded their ability to issue positive coverage policies.

This study adds to the body of literature by providing the current status of ES coverage in 160 million lives (~50% of the US population), a historical perspective of coverage from 2015 to 2017, and a description of the evidence used by payers for coverage policies in a detailed manner. Together, these data show a wide variability in quantity and quality of the evidence included for evaluation. The study demonstrates the need for systematic evaluation of evidence regarding ES (and other multigene panels) in coverage policies to gain a better understanding of the payer decision-making process.

Limitations

Our study's main limitation is that it only includes publicly available coverage policies from the largest private insurers. Because Medicaid covers almost half of births in the United States,[17] future analyses looking at publicly available Medicaid coverage policies will be informative and necessary. However, our analysis did cover 48% of the covered lives (160 million) in the United States. Second, we were limited by the amount of information provided in the coverage policies by each payer, which were highly variable in their detail and clarity. We could not examine the actual evidence selection and review processes undertaken by individual payers. Third, published payer coverage policies do not necessarily reflect actual coverage or reimbursement for all "covered" tests as plan purchasers can elect to exclude coverage for certain tests when purchasing plans for their employees. This is particularly true for self-insured groups, where the insurer acts as a third-party administrator. Furthermore, we did not evaluate the strength of evidence from each of the individual studies that were cited by each payer. Finally, nearly half of the payers analyzed were Blue Cross Blue Shield plans, though not all of the Blue Cross Blue Shield plans covered ES (5 positive coverage/3 negative coverage). Each plan may make independent coverage policies or their actions may be interdependent in ways that are unknown to us as researchers.

Conclusions

In sum, we found that coverage of ES increased from 2015 to 2017 and that there was variability in the number, type, and favorability of the citations. We conclude that more systematic assessments of the evidence used in coverage policies can help provide a greater understanding of coverage policies and how evidence is used, which in turn will facilitate the ability of clinicians to provide the most appropriate testing for their patients.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (https://doi.org/10.1038/s41436-018-0043-3) contains supplementary material, which is available to authorized users.

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DISCLOSURE

Dr. Phillips has received honoraria for serving on a scientific advisory panel and is a paid consultant to Illumina. Disclosures have been reviewed by the University of California–San Francisco. Mr. Douglas is a paid consultant to Illumina. The other authors declare no conflicts of interest.

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