InformedDNA®

Genetics, Decoded.

A Novel Approach to Evaluating the Utility of Genetic Tests: A Coverage Decision Framework™

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Introduction

While the explosion of efforts to advance precision medicine means ever increasing options for genetic testing, the potential benefit for patients is jeopardized by the pace of new test development and marketing--so rapid it frequently exceeds the rate of published evidence regarding a test's clinical utility. This ultimately leaves providers and payers in the position of reacting to test development and marketing trends without sufficient evidence or tools to evaluate utility.

There are three main barriers to applying a traditional clinical utility framework to genetic testing:

- **Lack of systematic oversight of genetic testing**
  Laboratory certifications such as Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) help establish a general level of acceptable laboratory performance and analytic validity, without addressing clinical utility. In addition, a majority of genetic tests on the market are laboratory-developed tests not subject to Food and Drug Administration (FDA) oversight. Given this landscape, there is immense variation in the quality and utility of clinically available genetic tests. In addition, because genetics is such a fast-moving field and incorporated into so many fields of medicine, there are often conflicting, lagging, or insufficient professional society recommendations regarding genetic testing.

- **Unique characteristics of genetic diseases**
  Historically, evidence frameworks were solely focused on the quality and quantity of clinical research trials and did not account for other factors relevant to genetic testing including rarity of the disease, rate of variants of uncertain significance in results, and differences between somatic and germline testing. The evaluation of the utility of a genetic test is more complex and nuanced than other areas of medicine due to these and other factors such as psychosocial impact, benefit to family members, and financial risks and benefits.

- **Advances in testing technology**
  Previous frameworks for the assessment of clinical utility of genetic tests were designed to assess one gene at a time. However, rapid advances in next-generation sequencing (NGS) technology have dramatically changed the landscape of commercially available tests such that the vast majority of genetic tests on the market now are multi-gene panels which do not lend themselves well to assessment models designed around single gene tests.

The ideal solution to address these concerns should incorporate a transparent and uniform approach that remains adaptable to the fast-paced evolution in the field of genomics. It would incorporate the relevant additional factors required for medical coverage decision making and laboratory contracting. After review and assessment of gaps in existing frameworks, InformedDNA® has developed a novel Coverage Decision Framework™ to facilitate clinical utility evaluation tailored to the field of genetic testing that will improve flexibility, transparency, and consistency in the evaluation of genetic tests and produce clear guidance for specific coverage decisions.

Summary of Existing Frameworks

Several existing models of evidence review were examined for their applicability to review of genetic tests. Below we comment on aspects that informed our development process for the InformedDNA Coverage Decision Framework.

PICO

In order to adequately answer questions regarding clinical utility, it is imperative to initially formulate and frame a well-focused clinical question of relevance. This assertion led to the evaluation of the PICO (patient problem, intervention, comparison, outcome) model which is a means of identifying the key question(s) of interest in order to minimize the potential impact of extraneous data driving the analysis and ultimate conclusion when it doesn't directly answer the relevant research question (Schardt et al. 2007; Richardson et al. 1995). Depending on the clinical scenario, formulating the relevant question(s) may have varying degrees of difficulty. However, several studies have demonstrated that using a PICO model helps to identify pertinent information to guide clinical decision making (O'Sullivan et al. 2013; Villaneuva et al. 2001; Schardt et al. 2007).

ICER

The Value Assessment Framework developed by the Institute for Clinical and Economic Review (ICER) takes a sophisticated population-level approach in the consideration of evidence, cost-effectiveness and contextual items to provide health technology assessments through a process grounded in multi-stakeholder engagement. While the benefits of their robust engagement are noteworthy, it typically results in a months-long production time for final report generation that is not optimal in the rapidly paced genetic testing field. One particular facet of the assessment, the Evidence Review Matrix, has been purported to be flexible enough for evaluating diverse interventions like genetic testing, and thus warrants consideration (Ollendorf and Pearson 2017).

ICER's evidence review process, while recognizing the strength and importance of randomized controlled trials, also allows for inclusion of multiple other sources of

evidence. The quality of each study is assessed and data is examined to analyze effectiveness, as well as adverse and other potentially important outcomes so that an estimate of the magnitude of net health benefit relative to the comparator can be assigned. The level of certainty, based on the strength of evidence is then provided as "conceptual confidence intervals," not through the use of mathematical algorithmic equations, but rather by the evaluation of different domains grounded in principles by the U.S. Preventive Services Task Force (USPSTF), Agency for Healthcare Research and Quality (AHRQ), and GRADE Working Groups. Finally, a rating is provided for the intervention via a specific letter grade to reflect the combined level of certainty coupled with the magnitude of comparative health benefit (Ollendorf and Pearson 2017).

Important questions of the reproducibility and validity of ICER's approach have been raised because it inevitably incorporates certain value judgments (Alliance for Patient Access 2019). ICER addresses this through transparent and thorough documentation of the rationale behind decisions, as well as the potential need for differential weighting of the various domains used. While reproducibility is a tenet of scientific study, it may be argued that it is reasonable and necessary to allow for judgment in applying differential weighting to certain domains based on the circumstances and evidence available. The nuanced approach necessary to evaluate clinical utility for genetic testing and treatment of rare disease was recently addressed by ICER. Through deliberations and public hearings, a decision was reached to include additional contextual explanation for applying their standard process to the assessment of treatments for rare disease instead of utilizing a separate protocol (ICER November 2017).

IHI

The Institute For Healthcare Improvement (IHI) is a not-for-profit think tank focused on improving healthcare both in the United States and abroad. In 2007, they developed their TripleAIM framework (Martin et al. 2007) focusing on the following three ideals: (1) Improving the patient experience; (2) Improving healthcare of the population; and, (3) Reducing the per capita cost of healthcare. Although the framework was designed to measure broader healthcare systems, it does offer some precedent for InformedDNA's approach that includes methods for reviewing drivers beyond evidence of clinical utility and improved patient outcomes.

EGAPP

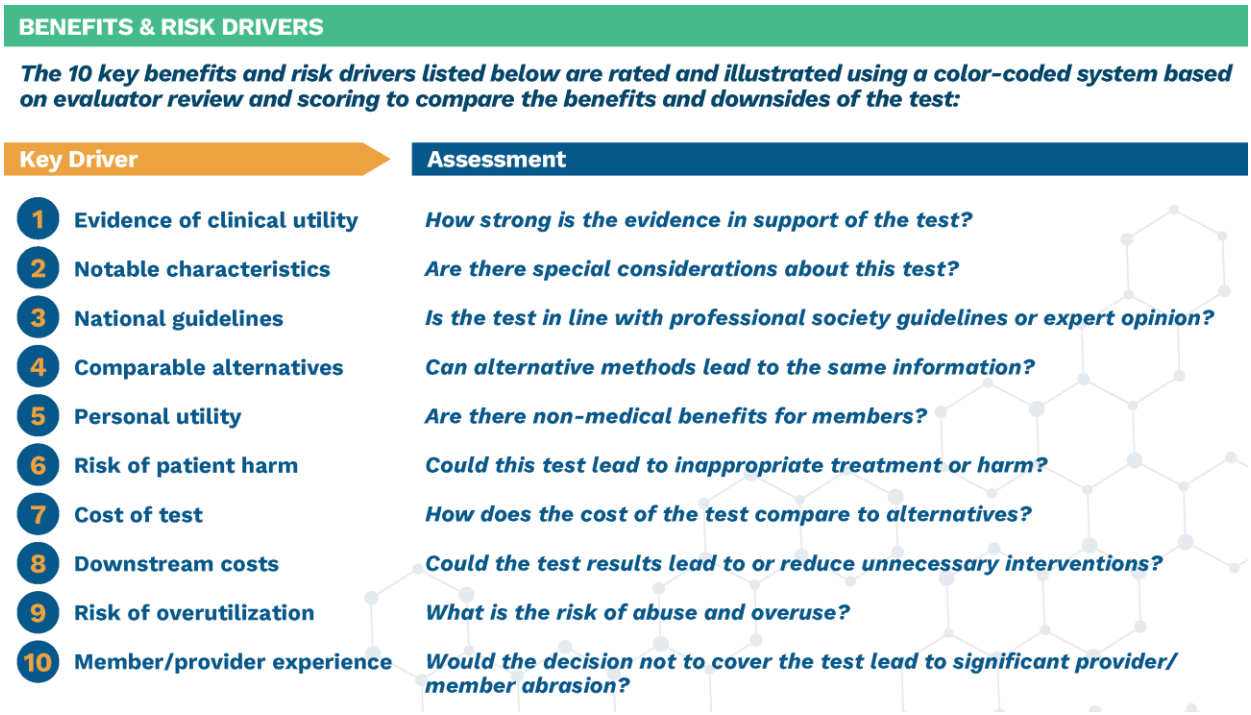
The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, comprised of subject experts in laboratory and clinical genetics, policy, health technology assessment, ethics and economics, was launched by the Centers for Disease Control and Prevention in 2004. Their primary intent was to develop methods

and standards that could be followed by others to develop evidence-based recommendations on genetic testing. To this end, they published two methods papers (Teusch et al. 2009; Veenstra et al. 2013) and a retrospective analysis of their work (EGAPP 2014). The EGAPP methodology builds on other well-established evaluative models, such as the USPSTF, AHRQ, and the CDC's previous process (ACCE), to systematically grade evidence for the clinical utility, clinical validity, and analytical validity of genetic tests and translate that information into clinical recommendations. Aspects adopted from ACCE include the formal assessment of analytic validity, consideration of ELSI, inclusion of data from unpublished "grey" literature, and use of key questions.

InformedDNA Coverage Decision Framework™

The InformedDNA Coverage Decision Framework was designed after analyses of existing assessment tools revealed several gaps: The ability to incorporate more variables (drivers), accommodate multiple stakeholder goals with flexibility and timeliness, offer transparency, afford consistent application, and provide clear guidance toward coverage decisions. As part of the approach, an illustrative technical description summarizing the test, process, and validation data is provided to stakeholders as well as detailed background information and a depiction of the current standard of care. The final result is a comprehensive report.

The Coverage Decision Framework mirrors the PICO model in first defining the patient population most likely to benefit and the clinical indication(s) (one test may have several assessments if utilized for multiple clinical indications). The following ten key benefit and risk drivers are then scored using a color-coded system to compare the risks and benefits of the test:



Each benefit/risk driver is thoroughly evaluated and scored as follows:

- High: Depicted with green color reflecting an assessment that is better than the current standard of care;
- Medium: Depicted with a yellow color reflecting an assessment that is comparable to current standard of care;
- Low: Depicted with a red color reflecting an assessment that is worse than current standard of care.

Figure 1. Benefit/risk driver scores.

Figure 2 below summarizes the benefit drivers and scores for each driver following an assessment of a test, “Genetic Test A”, currently available on today’s market. The drivers are described in more detail starting on page 9.

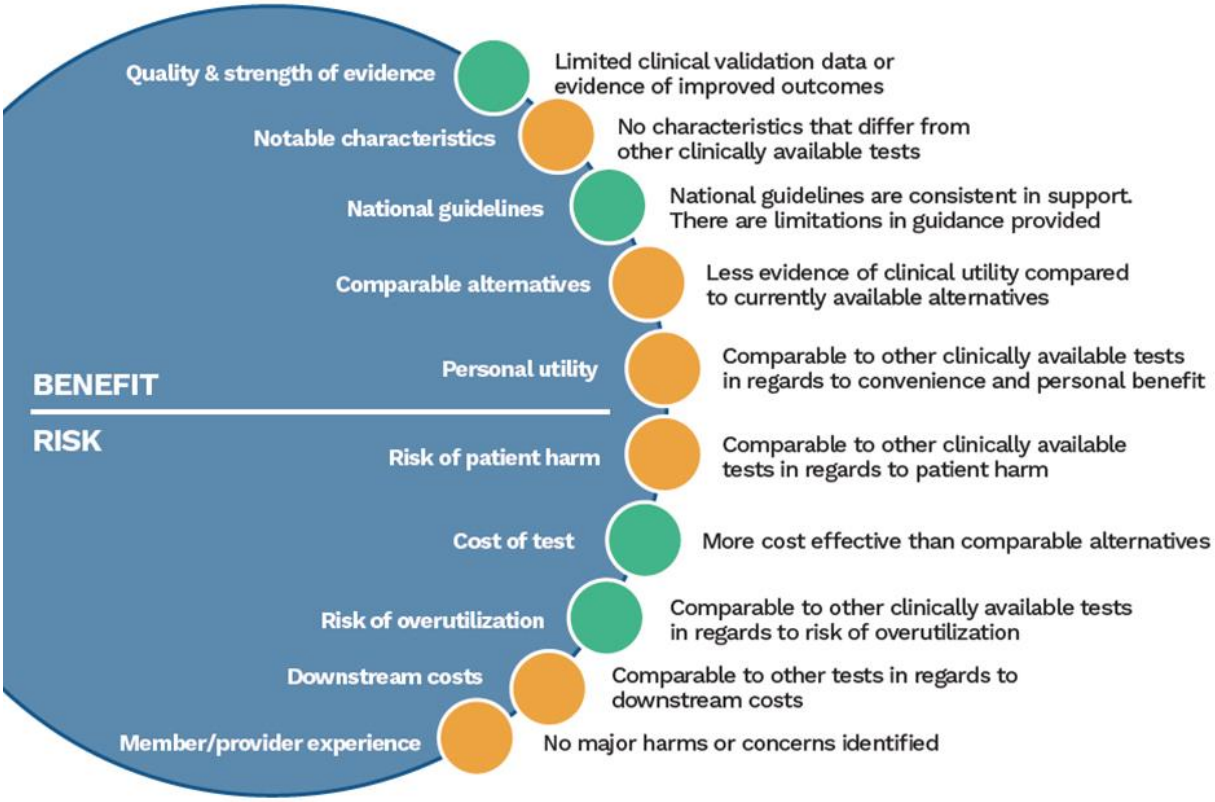


Figure 2. Risk Drivers and Corresponding Risk Driver Scores for “Genetic Test A.”

The final recommendation produced by the Coverage Decision Framework incorporates the information captured through individual driver analysis and allows delineation of any restrictions or considerations to coverage.

The combined net benefits and risks from the driver evaluation are demonstrated via a 3 x 3 graphic plot along with a recommendation category of: “Strongly recommend coverage,” “Recommend coverage,” “Consider coverage with restrictions” or “Do not recommend coverage.” This allows for a more nuanced discussion of the benefits and risks to coverage.

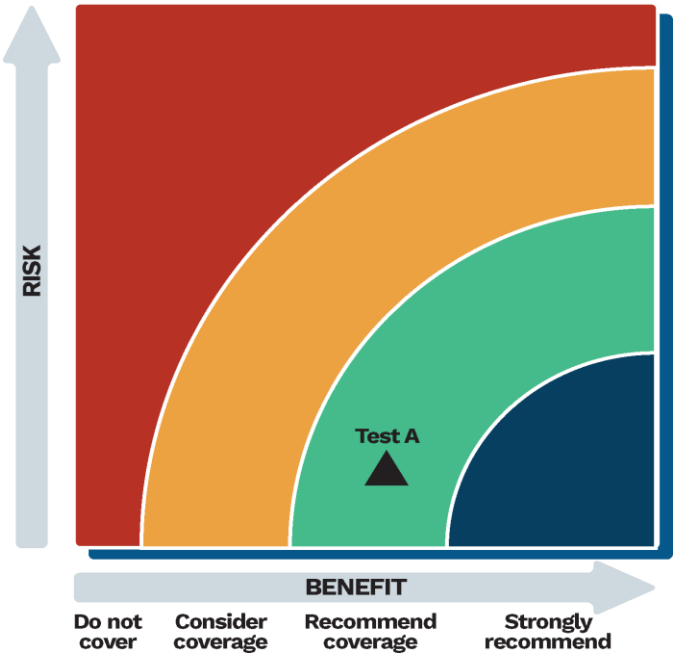


Figure 3. Coverage Decision Framework Coverage Recommendation for "Genetic Test A": *Consider coverage with restrictions*.

Individual Drivers

Driver #1: Quality and Strength of Evidence

While this framework considers non-traditional drivers, an important pillar of our assessment continues to be the critical appraisal of the literature supporting a traditional definition of clinical utility. The driver evaluating the quality and strength of evidence captures many of the steps encompassed by traditional methods for assessing clinical utility: (1) Framing the Review, (2) Identifying Evidence, (3) Evaluating Studies, (4) Summarizing Evidence, (5) Grading the Body of Evidence, and (6) Assigning a Clinical Utility Score. This approach allows the evaluator to determine the strength of the evidence in support of the test in the context of assessing the feasibility and potential limitations of performing high quality studies on the population of interest.

Framing the Review

A broad range of outcomes exist for genetic tests, thus an evidence review process should begin with recognizing potential outcomes. This includes whether an outcome is objective and straightforward to measure, such as survival, or instead reflects an indirect outcome or endpoint. As evidence is compiled and reviewed, care is taken to note what outcomes are being used to demonstrate or infer clinical utility. Ranking of

outcomes may also be utilized to allow for proportional weighting based on their perceived importance as suggested by Botkin et al. 2010.

Identifying Evidence

Once the analytic framework and outcomes of interest have been defined, relevant evidence is collected and analyzed, including peer-reviewed literature as well as data extracted from “grey” literature, e.g. FDA package inserts, conference abstracts/proceedings/presentations and government publications. Search methods, criteria for inclusion/exclusion, and delineation of evidence gaps are documented to provide transparency regarding each assessment.

Evaluating Studies

A number of paradigms exist for evaluating the quality of evidence for genetic testing. The process incorporated for the Coverage Decision Framework is derived from the EGAPP method for clinical utility assessment (Teutsch et al. 2009), as it defines a transparent and analytical framework incorporating elements of other well-established evaluative models, but is designed specifically for genetic testing.

Evaluation of individual studies involves ranking the overall study design, analyzing study methodology for threats to internal validity, and assessing external validity by reviewing the study population to ensure it is applicable. The hierarchy of study designs provides utility in describing and comparing data sources, but it’s important to note that a highly ranked yet poorly executed study may provide less compelling evidence than a lower ranked but well-executed study.

Summarizing Evidence

A summary of evidence table, adapted from the USPSTF, is constructed to provide a clear representation of the data assessment related to the clinical utility of a genetic test.

Grading the Body of Evidence

Once evidence has been identified and summarized, an assessment is made to determine whether the quality of evidence is adequate to support confident conclusions about the clinical utility of a genetic test, again, using a system modeled after the EGAPP Working Group methods (Teutsch et al. 2009). Gaps in evidence, e.g. for emerging technologies and potentially promising tests with insufficient data, are articulated and the literature periodically re-evaluated.

Assigning a Clinical Utility Score

The process of evidence evaluation culminates with the assignment of a clinical utility score (“no evidence of clinical utility or strong evidence against clinical utility”; ”moderate/weak evidence of clinical utility”; “conflicting evidence of clinical utility”;

"high quality/strong evidence of clinical utility"). While there is an inherent degree of subjectivity to scoring, transparency is maintained through documentation of rationale and clear presentation of the evidence supporting the score.

Driver #2: Notable Characteristics

Laboratories often market their genetic tests as having unique or exceptional properties that add value. Significant differences may exist between similar genetic tests while at the same time the difference in their clinical utility may be negligible. On the other hand, there may be notable characteristics of a test that set it apart from comparable alternatives. This driver attempts to evaluate these test attributes, which may be difficult to assess in a traditional approach to measuring clinical utility. Examples of notable characteristics include novel methodology requiring less invasive procedures, ability to determine eligibility for clinical trials, or improved turnaround time, patient satisfaction and quality of life. These factors may not ultimately be incorporated into medical necessity criteria, but may be important considerations in the overall assessment of available testing options and their clinical utility. This driver allows notable characteristics to be taken into consideration, but does not penalize a test lacking such attributes.

Driver #3: National Guidelines

This driver evaluates to what extent the test or technology is supported by clinical practice guidelines produced by various professional organizations at the national and international levels. Incorporating a driver on National Guidelines is vital to appropriately focus on the intended population(s), intervention and comparison/outcome(s) that ultimately impact clinical management of patients (Guyatt et al. 2008). Relevant guidelines are identified and care is taken to select those with defined key components resulting in high-quality and trustworthy recommendations. There has been concern about the lack of transparency in the development of guidelines as well as the evaluation of the data referenced (Graham et al. 2011). It is important to recognize that recommendations relevant to genetic testing and the detail provided may vary widely due to the differences in relevant populations, purposes and methodologies. Published guidelines may provide discordant recommendations due to variability in factors such as the disorder/condition addressed and composition and perspectives of the working group.

It has also been noted in the medical literature that there is a dearth of appropriate tools available for assessment of guidelines for fields such as genetics (Zeng et al. 2015). Burke et al. (2019) provide further commentary on this issue. They propose, in the absence of robust evidence, temporary advice delineated as standardized clinical practice advisory documents (CPADs) that can provide a needed framework for consistent clinical decision-making while identifying evidence gaps to facilitate critical research in order to support the appropriate use of emerging genomic

technology and testing (Burke et al. 2019). These CPADs could be launched using foundational elements already published in advice documents from organizations such as the American College of Medical Genetics (ACMG), the National Society of Genetic Counselors (NSGC) and other relevant professional societies. They can be re-examined periodically to determine if evidence has surfaced to move the CPAD along the trajectory of provisional evidence to formal clinical practice guideline (CPG) recommendations.

Several of our Coverage Decision Framework drivers mirror key elements proposed for CPADs, and InformedDNA's genetic analysts identify evidence gaps and nuances in current available clinical practice guidelines when assessing this driver. Key factors used to score this driver include whether or not FDA approval has been granted and whether currently available professional society guidelines recommend against the test, do not include the test, contain weak or conflicting support, or reveal high concordance and strong evidence for testing.

Driver #4: Comparable Alternatives

Phillips et al. (2017) defined the use of Comparative Effective Research (CER) in genomic medicine as "measuring the clinical utility of using genomic information to guide clinical care and impact patient outcomes in comparison to appropriate alternatives that may or may not include genetic testing". The authors provided a summary of systematic reviews of CER specific to genomic medicine and found that most reviews include a specific list of comparators including genetic testing, no testing, and other criteria or risk scores. While the authors noted broadly that there is limited data on the impact of genetic testing on health outcomes, they identify a list of important concepts to consider, many of which have been incorporated into the InformedDNA Coverage Decision Framework.

A recent search of the NIH clinicaltrials.gov web site for "Standard of Care" within active and/or recruiting clinical trials identified more than 4,000 studies involving a comparison with standard of care. Such CER studies may involve comparison of a new treatment/test to standard of care or may involve comparison of two widely accepted treatments/tests to one another. The American Society of Clinical Oncology (ASCO) advocates for raising expectations for clinically meaningful outcomes for patients through clinical trial design and notes that reporting small gains in outcomes may not be sufficient (Meropol et al. 2001; Ellis et al. 2014). Additional emphasis is placed on identifying appropriate study endpoints to measure clinical impact of testing and that this may change as the standard of care changes. While ASCO notes these guidelines are not meant to be used for regulatory approval or insurance coverage, the concepts of clinically meaningful outcomes is essential to any coverage assessment framework.

Including comparable alternatives as a driver within InformedDNA's framework aligns with the current emphasis within the medical literature on comparative effective research and identification and reporting of clinical meaningful outcomes. This driver specifically lists current clinically available alternative strategies and tests that provide similar information in terms of gene content, target population, and/or overall purpose of the test under review. Comparisons are made to standard of care or other similar tests rather than no testing, unless no testing is the current standard of care. Relevant parameters are employed to ensure equitable and consistent comparisons such as appropriate endpoints (e.g., progression free survival versus overall survival); novelty in technology or performance characteristics; clinical availability and desirability of alternatives.

Driver #5: Personal Utility

While genetic testing offers patients many traditional medical benefits, a unique hallmark is its provision of additional psychosocial and familial benefits that can be equally important and useful to patients. A genetic test result may provide information about risk for family members or a unifying diagnosis for a constellation of variable symptoms among family members not previously recognized as related. A genetic test result may also lead to identification of relevant advocacy and resources offering needed support, such as for a family newly dealing with a known (and sometimes rare) diagnosis (Niguidula et al. 2018; Martin et al. 2018). "Personal utility" encapsulates these unique and relevant aspects of genomic medicine that are important to consider in assessment of genetic tests.

Multiple articles have described non-medical benefits of genetic testing that provide personal utility. Kohler, Turbitt, and Biesecker (2017) performed a literature review to determine what constituted personal utility in a variety of genetic tests and found it included elements such as emotional impact, affects on personal well-being, impact to practical affairs, and impact on support systems. Phillips et al. (2017) use a similar definition of personal utility emphasizing the importance of including "patient-centered" considerations when evaluating genetic tests' impact on outcomes. Bunnik et al. (2015) emphasized that, in some scenarios, high personal utility and high clinical utility may align, and in others, a test may have high personal utility and low clinical utility. These investigations spotlight the abundant potential non-medical benefits for the patient when dealing with genetic testing and highlight the importance of the inclusion of this driver.

Driver #6: Risk of Harm

While genetic testing offers unique benefits, there is also the risk for adverse clinical outcomes or psychological harm. Multiple studies have elucidated the various risks of harm from genetic testing which include, but are not limited to: misinterpretation of test results (Bensend et al. 2014; Gollob 2017); challenges of variant interpretation

(Hallowell et al. 2002; Burns et al. 2017); and, inappropriate treatment and psychological harm including distress stemming from incidental findings (Macrae et al. 2013; Mand et al. 2013; Shkedi-Rafid et al. 2014).

This driver allows the evaluator to take into account the impact of the particular genetic test or technology's risk for harm. This is done by determining, among other factors, whether the test could lead to inappropriate treatment in a significant portion of the population tested, the risks for detecting variants of unknown significance, the potential difficulty of test interpretation for providers and/or patients, and the impact of potential psychological harm.

Driver #7: Cost of Test

While cost is not traditionally a determinant for evaluating the medical necessity of a genetic test, it is an important public health consideration and relevant for laboratory contracting purposes. Assessing the cost of genetic testing is complex and often difficult. Genetic test pricing is variable, and it is common to see multiple prices for a single test: a laboratory's listed price, a payer or institution's contracted price, and a cash-pay price. The analysis of this driver is intended to compare the direct costs of the requested test/intervention to the direct costs of standard of care testing. Other considerations, such as the feasibility of achieving favorable contracted rates for testing are taken into consideration.

Driver #8: Risks of Overutilization

Risk of overutilization, or abuse, has been documented across all facets of medical interventions including genetic testing. This driver assesses the risk of the test being used in an individual (or a population) for reasons not specific to the patient's indication, i.e. likelihood of over-testing. One must first consider the scope of the patient population for which the test is likely indicated prior to assessing whether the test meets the definition of clinical utility for this population. Tests may meet appropriate guidelines for one population, but not for another. Even a test that has proven clinical utility in one setting may need additional scrutiny if it is being applied to a new population or has a new anticipated use in a specific population.

Another consideration is the condition's prevalence when assessing the risk for overutilization. Once the population most likely to benefit has been identified, additional risks can then be evaluated. In contrast, tests performed for a wide range of patient indications (or based on no/minimally defined criteria) or tests performed without regard to the prevalence of the condition likely lack a defined population for which the test is considered to have utility. This further hinders efforts at assessing risks of overutilization.

Unique marketing and advertising considerations may also be a factor in risk for overutilization. Certain tests such as a pan-cancer multi-gene panel may be heavily marketed as desirable for many indications, while ignoring important questions related to clinical utility. As Braverman, Shapiro, and Bernstein (2018) state, a "...discrepancy between professional society guidelines and market realities" influences both physicians and patients who now are presented with broader options for genetic testing and wider access to testing. Irresponsible advertising may even extend to promoting the use of a test for what may be considered an "off-label" indication.

Similar results were noted in a survey of laboratories' websites offering expanded carrier screening for reproductive planning purposes (Chokoshvili et al. 2018). Results revealed common reference to benefits and ample details available about positive results, with less attention to concepts such as implications of a negative result, limitations of the screening for other (i.e., chromosomal) conditions, genes with known reduced penetrance, how the test aligns with national professional society's practice guidelines, and the potential for false positive or false negative results.

Examples in the medical literature demonstrate how the dangers of over-testing can occur in the setting of genomic medicine. These have potentially far-reaching impact on efforts to provide coverage for those in need and on efforts to promote appropriate genetic testing and genetic education among those receiving testing. Gill, Obley, and Prasad (2018) describe a scenario where an increase in testing following a high-profile celebrity experience did not correlate with an increase in the use of related health services, reflecting that those undergoing testing were self-selected due to raised awareness of the test and not because they had relevant risk factors warranting the test. Their second example noted an increase in testing following a laboratory's advertising campaign for a test - with data showing that more than half of those tested were not high-risk. Kalokairinou et al. (2017) go so far as to state that over-testing poses a risk for "adverse impact on public health" after delineating how marketing/advertising of genetic tests is inherently biased toward the sale of a product or service.

These examples highlight the potential for the abuse of genetic testing and its impact on patient care, making it a consistent consideration in InformedDNA's Coverage Decision Framework. Factors considered in evaluating this driver include the marketing strategy, scope, and accuracy as well as the prevalence of the condition for which the test is sought and how well the indication for testing is defined.

Driver #9: Downstream Costs

This driver estimates the potential increase or decrease in downstream costs (e.g., follow-up testing, ongoing screening/visits, procedures, treatments) resulting from genetic testing results. Several factors must be taken into consideration during its

evaluation, including the lack of published literature and standardization in the estimation of such costs. The trend towards broad-based genomic testing versus targeted testing also raises the complexity of this issue (Christensen et al. 2018). The estimation of downstream costs for broad genomic profiling may cover the span of a person's lifetime and is hindered by difficulties in obtaining “true” costs over this timespan, including advances in technology/knowledge/medical management which alter the analysis. Therefore, the impact of testing on downstream costs is most reliably estimated in the short term based on the localized impact and may not accurately reflect long-term cost outcomes. Points for consideration in evaluation of this driver include: Impact on tangible outcomes such as genetic testing eliminating the need for further surveillance in some patients; genetic test results leading to surveillance of uncertain benefit; and, genetic testing leading to significant off-label drug prescription.

Driver #10: Member/Provider Experience

Genetic tests may become heavily utilized prior to publication of clear evidence of clinical utility. This driver evaluates external pressures for coverage observed when providers, members, or laboratories accelerate unwarranted test uptake in advance of solid evidence. The ultimate recommendation to restrict a genetic test that has already garnered a high expectation of coverage may lead to significant provider-payer abrasion. If coverage decisions conflict with actual or perceived best practices, providers may experience pressure to offer services to which limit perceived liability and/or align with peer groups. Assessment of this driver permits anticipatory guidance and better justification for policy decisions.

Laboratory efforts and competition to provide administrative support services may impact provider preferences, as providers often report a lack of comfort with genetic testing-related knowledge (Hamilton et al. 2016) and may factor in the value of clinical support from the performing laboratory when considering a particular test. Providers’ expected level of test utilization is an important consideration when evaluating potential impact of a coverage decision.

Conclusion

While multiple frameworks exist today for evidence review, few, if any solutions have emerged that address all facets of genetic testing. InformedDNA’s Coverage Decision Framework fills this void by providing a systematic, efficient and reproducible mechanism to assist provider and payer decision making in today’s landscape of genomic medicine. The use of multiple risk/benefit drivers prompts systematic assessment of the unique aspects of multi-gene panel testing, alleviating the increasingly frequent coverage predicaments brought on by the rapidly growing number of tests in today’s marketplace. While there remains a lack of systematic

oversight for the majority of genetic tests on the market, genetics professionals have successfully tackled development of other guidance resources for the fast-paced realm of genomic medicine (Burke et al. 2019).

As methods for evaluating evidence and measuring clinical utility advance, the InformedDNA Coverage Decision Framework will continue to evolve to meet current marketplace needs. In the interim, this model provides a mechanism to address the unique challenges related to genetic testing and the fast-paced demands for coverage decision recommendations. The framework produces transparent coverage recommendations supported by evidence that is clearly illustrated. The InformedDNA Coverage Decision Framework stands alone in its flexibility to accommodate multiple stakeholder considerations and goals and provide clear guidance toward coverage decisions.

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