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Genetic Testing for Developmental Disabilities, Intellectual Disability and Autism Spectrum Disorders

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The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In clarifying the scope of work for this Technical Brief, the authors consulted several Key Informants who represent clinicians, patients, payers, professional societies, and genetic test researchers. The Evidence-based Practice Center (EPC) sought input on the priority areas for genetic testing and developmental disabilities. Key Informants are not involved in data analysis or the writing of the report. Therefore, the content of the report does not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users and their expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants will be added to the final report.

Contents

Tables

Figures

Appendixes

Structured Abstract

Background: Genetics research in recent decades has discovered numerous genetic markers that may explain the etiology of developmental disabilities (DDs). Genetic tests (e.g., array comparative genomic hybridization, sequencing) are rapidly diffusing into clinical practice for diagnosing DDs or, more often, for determining their genetic etiology. An urgent need exists for a better understanding of these tests and their clinical utility.

Purpose: This Technical Brief collects and summarizes information on genetic tests that are clinically available in the United States to detect genetic markers that indicate DDs. It also identifies existing evidence addressing the tests' clinical utility. This Brief primarily focuses on patients with idiopathic or unexplained DDs, particularly intellectual disability, global developmental delay, and autism spectrum disorder. Several better-defined DD syndromes, including fragile X syndrome, Rett syndrome, Angelman syndrome, Williams syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Smith-Magenis syndrome, and velocardiofacial syndrome, are also included. Patient-centered health outcomes (e.g., functional or symptomatic improvement) and intermediate outcomes (e.g., changes in clinical decisions or family reproductive decisions, the tests' diagnostic accuracy and analytic validity) are examined.

Methods: We sought input from eight Key Informants to identify important clinical, technology, and policy issues from different perspectives. We searched the National Center for Biotechnology Information's Genetic Testing Registry (GTR) to identify genetic tests. A systematic search of studies published since 2000 was performed to identify available evidence that addresses genetic tests' clinical utility.

Findings: Our search of the GTR database identified 727 laboratory-developed tests offered by 64 providers in 29 States. We also identified one test cleared by the U.S. Food and Drug Administration. Common analysis methods used in the tests include array comparative genomic hybridization, microarray, sequencing, and polymerase chain reaction. We did not identify any study that directly assessed genetic testing's effects on health outcomes. Most of the clinical studies identified for indirect assessment of clinical utility are case series reporting on a test's diagnostic yield.

Background

Recent decades have witnessed numerous advances in genetics research highlighting the importance of genetic factors as an etiology for developmental disabilities (DDs). Given the rapid diffusion of advanced genetic tests for diagnosing DDs or determining their etiology, the Agency for Healthcare Research and Quality (AHRQ) commissioned the ECRI Institute–Penn Medicine Evidence-based Practice Center to prepare this Technical Brief to provide an overview of these tests. The brief is intended to collect and summarize information on tests that are clinically available in the United States (refer to the guiding questions in a later section for the type of information we collect). The brief is also intended to identify existing evidence addressing the clinical utility of genetic tests for DDs. An evidence map is presented to outline evidence gaps on the subject and provide guidance for future research.

Developmental Disabilities

DDs are a group of conditions associated with functional impairment in physical, learning, language, or behavior areas.[1] According to this definition, the Centers for Disease Control and Prevention (CDC) categorizes a broad range of conditions as DDs, such as attention-deficit/hyperactivity disorder, autism spectrum disorder (ASD), cerebral palsy, hearing loss, learning disability, intellectual disability (ID), Tourette syndrome, vision impairment, and others.[1] The prevalence of DDs is estimated to be more than 15 percent in children 3–17 years of age.[2] These disorders, which can often require lifelong individual and family support or treatment, have a profound impact on patients, families, and society.DDs can be caused or influenced by a variety of genetic and environmental factors, including gene mutations, mother's health behaviors (e.g., smoking and drinking), complications during pregnancy or birth, and the exposure of the pregnant mother or child to environmental toxins.[1] The causes of some developmental disabilities (e.g., Down syndrome, fragile X syndrome, fetal alcohol syndrome) have been well understood. However, the underlying causes of many other DDs (e.g., ASD, ID) are often unclear and may vary substantially across individuals.

DDs can affect cognitive, motor, and/or sensory functions. This Technical Brief focuses on genetic tests for evaluating DDs with primarily cognitive impairments, including nonsyndromic ID, ASD, and global developmental delay (GDD). Additionally, several DD syndromes were also included in this report based on input from key stakeholders. These syndromes include fragile X syndrome, Rett syndrome, Angelman syndrome, Williams syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Smith-Magenis syndrome, and velocardiofacial syndrome. Manifestations of GDD, ID, or ASD might be the main reason for the families to seek evaluation or care for patients with these syndromes. DDs primarily diagnosed by overt physical anomalies or that predominantly involve basic sensory or motor impairments (e.g., cerebral palsy, hearing loss, vision impairment) are beyond the scope of this brief.

Intellectual Disability and Autism Spectrum Disorders

ID is a DD that may present in infancy or early childhood years. The American Association on Intellectual and Developmental Disabilities (AAIDD) defines ID as "a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills."[3] ID affects 1 to 3 percent of the population worldwide,[4,5] and about 0.7 percent of children aged 3 to 17 years in the United States.[2] Clinically, ID is diagnosed using standardized measures of developmental skills. These measures

cover the domains of intelligence (IQ), adaptive behavior and language function.[6,7] Because these standardized measures may be less reliable and valid for children younger than 5 years of age, establishing the clinical diagnosis of ID in early childhood can be difficult.[3]

Some possible causes that have been linked to ID include genetic or chromosomal aberrations, exposure to harmful substances (e.g., alcohol) or infection during pregnancy, complications during birth, acquired brain injury, and preterm birth.[8] Currently, there is no cure for ID. Management of ID includes family support, family education and counseling, and special educational programs that may begin as early as infancy.[9] The goal of treatment is to develop the child's full potential.

ASD is a complex neurodevelopment disorder, characterized by social interaction and communication impairment and restricted, repetitive, and stereotyped patterns of behavior. ASD varies in character and severity. In the period from 2006 to 2008, studies reported that autism affected 0.74 percent of children aged 3–17 years in the United States.[2] In 2010, the Autism and Developmental Disabilities Monitoring Network sites reported that the prevalence of ASD among children aged 8 years was 1.47 percent.[10] Both genetic and environment factors (e.g., maternal valproic acid use during pregnancy, congenital rubella) may play a role in ASD development,[11] and multiple genes have been found to influence ASD risk.[12]

ASD diagnosis is based on interviews with the child and family, a review of records and historical information, and examination of the child using standardized instruments (e.g., Autism Behavior Checklist, Autism Diagnostic Interview-Revised) to demonstrate presence of core features of ASD. The history and examination are conducted using the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria.[13] The diagnosis of autism in infants and very young children is more difficult because developmental and behavioral assessment of these children may be more challenging. Some core features (e.g., socialization deficits or stereotyped movements) may emerge later as the child develops.

Currently there is no cure for ASD. Key treatments include structured educational and behavioral interventions (e.g., Applied Behavioral Analysis) to address core and associated symptoms and to promote development of social and language skills. Behavioral interventions and medication may be used to address comorbid symptoms (e.g., anxiety, depression) or severe behavioral problems (e.g., aggression, self-injurious behavior).

Because establishing a diagnosis of ID or ASD may be challenging in infants and very young children, a term, global developmental delay (GDD), is often used to categorize children who are younger than 5 years of age who have a significant delay in two or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living.[3,14] Significant delay is defined as performance two standard deviations or more below the mean on age-appropriate, standardized normal referenced testing.[15] Evaluating developmental delays requires accurate documentation by using norm-referenced and age-appropriate standardized measures of development administered by experienced developmental specialists.[3,15] Although GDD suggests a possible future diagnosis of ID and/or ASD, a child with GDD is not necessarily destined to have those conditions.

The prevalence of GDD is unknown, but may be similar to that of ID and ASD. GDD has a heterogeneous etiologic profile and is associated with age-specific deficits in adaptation and learning skills. Both genetic and environmental factors may be associated with GDD.[15,16]

Genetic Testing for Developmental Disabilities

Genetic abnormalities have been linked to many DDs. Studies suggested that up to 40 percent of DDs may be caused by some genetic aberration.[17,18] Conventional G-banded karyotyping has been used for decades to confirm the diagnosis of DDs (e.g., aneuploidies) that have a well-defined genetic etiology. More recently, new genetic methods (e.g., microarray-based comparative genomic hybridization [aCGH] and sequencing) have been developed and used to detect genetic abnormalities associated with DDs. These newer tests support the examination of genetic information at a higher resolution and may show genetic abnormalities not seen on G-banded karyotyping. In Appendix B, we provide a detailed technical overview to help illustrate how these genetic testing methods work and the main differences between these methods.

As previously discussed, clinical diagnosis of ID, GDD, or ASD is typically based on clinical manifestations and cognitive and developmental assessment using standardized measures. The purpose of genetic testing in children with idiopathic or nonsyndromic ID, GDD, or ASD is to identify a genetic etiology. Proposed benefits of establishing an etiologic diagnosis include the following:[3,19-26]

- Clarifying a genetic cause and improving the psychosocial outcomes (e.g., improved sense of empowerment) for patients and their families
- Providing prognosis or expected clinical course
- Evaluating recurrence risks and helping families in reproductive decisionmaking
- Refining treatment options
- Avoiding unnecessary and redundant diagnostic tests
- Identifying associated medical risks to prevent morbidity
- Providing condition-specific family support
- Facilitating acquisition of needed services and improving access to research treatment protocols

Because of these potential benefits, genetic tests are being used at an increasingly rapid rate. Medical genetics groups now recommend chromosomal microarray analysis (CMA) as a first line genetic test to identify genetic mutations in children with multiple anomalies not specific to well-delineated syndromes, nonsyndromic DD/ID, and ASD.[3,19,21,27] Payers have seen a significant number of claims for genetic testing in children with alleged or proven DDs.[28] However, little evidence from controlled studies exists to directly link genetic testing to health outcomes.[29] Published studies have reported superior diagnostic yields of newer genetic tests (e.g., aCGH) in identifying DD-related genetic abnormalities, and some have identified the impact of the tests on medical management (e.g., medical referrals, diagnostic imaging, further laboratory testing).[20-26] However, these findings are not sufficient for drawing a conclusion that use of the tests will lead to improved health outcomes (further discussion on this issue is provided in a later section, Establishing the Clinical Utility of Genetic Tests).

The impact of increased utilization of genetic tests, such as CMA, on health care costs is unclear. Advanced genetic tests are generally more expensive to perform than conventional G-banded karyotyping or other clinical tests.[30] Identification of genetic abnormalities on germline cells may also lead to genetic testing in patients' relatives, which further expands the pool of children for testing and magnifies the potential impact. Conversely, the potential increased diagnostic yield of advanced genetic tests may reduce the number of other clinical tests or services used to identify genetic causes of DDs. Besides the uncertain clinical utility and

concerns about economic impact, ethical issues—such as how to deal with genetic abnormalities unrelated to DD that are detected in genome-wide CMA—also remain controversial.[31]

Availability of Genetic Tests for Developmental Disabilities in the United States

Genetic tests become clinically available in the United States via one of two pathways. A genetic test may reach the market as a commercially distributed test kit approved or cleared by the U.S. Food and Drug Administration (FDA) or as a laboratory-developed test (LDT).[32,33] Test kits cleared or approved by FDA include all reagents and instructions needed to complete the test procedure and interpret the results. These test kits can be used in multiple laboratories. LDTs are developed in laboratories using either FDA-regulated or self-developed analyte-specific reagents and are intended for performance solely in the test developer's laboratory.

The U.S. Centers for Medicare & Medicaid Services regulates laboratories that perform LDTs under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).[32,33] Under CLIA regulations, facilities that perform tests on "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" must obtain a certificate from the CLIA program. The requirements for CLIA certification are based on the complexity of the tests. LDTs compose the majority of the genetic tests that have become available to clinical practice.[33] Laboratories offering LDTs must be licensed as a high-complexity clinical laboratory under CLIA regulations. A technology assessment report suggested that genetic tests for diagnosing DDs are mainly available as LDTs.[29]

Historically, FDA has exercised regulatory enforcement discretion over LDTs because they were relatively simple lab tests. As LDTs become more complex and proliferated in clinical use, the agency is taking steps to actively regulate LDTs. On July 31, 2014, FDA notified Congress of its intention to publish two draft guidance documents in 60 days regarding oversight of LDTs, entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."[34-36] Under the proposed regulatory framework, LDTs will fall into one of the three categories: LDTs subject to full enforcement discretion; LDTs subject to partial enforcement discretion; and LDTs subject to full FDA regulation. Once the proposed FDA guidance documents are finalized, it will become clearer how genetic tests for DDs will be regulated and whether any current LDTs will still be available for clinical use.

Evaluating the Clinical Utility of Genetic Tests

The clinical utility of a genetic test refers to how likely the test is to affect clinical decisions and ultimately improve patient outcomes. The ideal type of evidence for establishing the clinical utility is from high-quality randomized controlled trials (RCTs) that compare use and no use of the test in clinical practice and analyze whether any significant differences in health outcomes occur between the compared arms. In reality, however, this type of RCT is rarely conducted.[32,33,37] To answer the ultimate clinical utility question—whether use of the test will improve health outcomes—an inference-based chain of evidence often needs to be established.[37,38] Establishing this chain of evidence involves assessing the analytic validity and clinical validity of the test of interest and establishing an indirect evidence link to clinical outcomes.

Analytic validity refers to how accurately and reliably the test measures the analyte of interest, such as a gene aberration. Analytic validity is a function of many factors such as analytic accuracy, precision, analytic sensitivity and specificity, reportable range of test results for the test system, and reference range or normal values. The technical terms for analytic validity are defined in Appendix C of this report, Definition of Terms.

Clinical validity, also known as diagnostic accuracy, refers to how accurately the test detects or predicts the clinical condition of interest. Clinical validity is usually described in terms of clinical sensitivity, clinical specificity, positive and negative predictive values, likelihood ratios, diagnostic odds ratios, and the area under a receiver operator characteristic (ROC) curve. These technical terms related to clinical validity are also defined in Appendix C of this report.

To establish the chain of evidence, an evaluation framework for genetic tests is typically used. An evaluation framework is a conceptual approach to evaluating tests and organizing the relevant evidence. The framework is a tool for clarifying the scope of the questions to be addressed in health technology assessment and the nature of evidence necessary for answering the questions. Different stakeholders (e.g., patients, providers, payers, regulators, and test developers) may need somewhat different frameworks for their evaluations. For this report, we used an evaluation framework that emphasizes patients' perspectives (Figure 1). This framework is from an Agency for Healthcare Research and Quality (AHRQ) methods report we authored on the evaluation of genetic tests. The framework delineates the relationship between analytic validity, clinical validity, and clinical utility and helps demonstrate areas in which evidence is available or missing.[37]

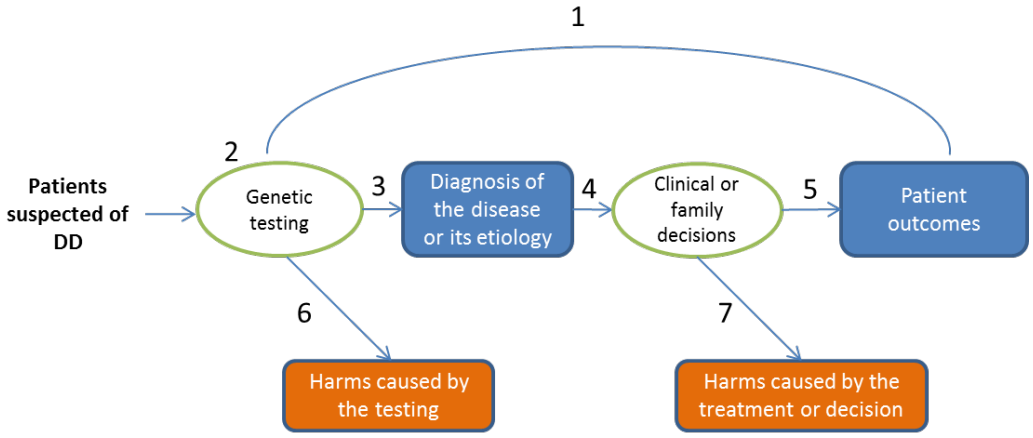
Under this framework, we address key research questions to establish the chain of evidence for clinical utility. These questions are as follows:

- Question 1: Does using a genetic test lead to improved health outcomes in patients with DDs compared to the standard-of-care diagnostic strategy?
- Question 2: Does the test have adequate analytic validity?
- Question 3: Does the test have adequate clinical validity?
- Question 4: Does using the test have any impact on treatment decisionmaking by clinicians or families?
- Question 5: Does the altered treatment lead to improved patient outcomes?
- Question 6: Are there harms associated with use of the test?
- Question 7: Are there harms associated with the altered treatment?

To address these key research questions, different types of evidence may be required. For example, to address the overarching clinical utility question, RCTs are most appropriate. To address question 3 regarding clinical validity, diagnostic cohort studies that use a gold-standard reference method are ideal.

Answering Question 1, the overarching question, is the ultimate goal of evaluating a test's clinical utility. When direct evidence does not exist or is insufficient to draw a reliable conclusion for this question, addressing other questions may provide indirect evidence on the likelihood of a test affecting health outcomes. For example, if evidence shows that a test does not have adequate analytic validity, then the test is not likely to have adequate clinical validity. If a test does not have adequate clinical validity, it will have limited impact on treatment or family decisions. If a test does not change clinical or family decisions, it is unlikely to affect health outcomes.

Figure 1. Evaluation framework for genetic tests for diagnosing DDs



Guiding Questions and Scope of Work

To meet this Technical Brief's objectives, we used a series of questions to guide our efforts in collecting appropriate information. These guiding questions fall in four categories:

1. Description of genetic tests for diagnosing or determining the etiology of DDs
    a. What genetic tests for diagnosing or determining the etiology of DDs are available for clinical practice in the United States?
    b. What genetic techniques or analysis methods (e.g., CMA, aCGH, subtelomeric fluorescence in situ hybridization) are used in these tests? How do these types of techniques or methods work?

2. Context in which genetic tests are used for diagnosing or determining the etiology of DDs:
    a. What is the regulatory status (i.e., FDA clearance or approval status, CLIA certification of the test provider) of the tests?
    b. What kinds of credentials (i.e., training, certification) are required for interpreting test results?
    c. Who are the providers ordering the tests and using their results?

3. State of the evidence on genetic tests for diagnosing or determining the etiology of DDs
    a. What are the DD conditions addressed in studies of these tests?
    b. What are the study designs used?
    c. What outcomes are reported?
        i. What data have been reported in the literature about the analytic validity of the tests?
        ii. What data have been reported in the literature about the clinical validity of the tests?
        iii. What data have been reported in the literature about the clinical utility of the tests?
        iv. What are the potential safety issues or harms related to the tests?

4. What are the important issues raised by genetic tests for diagnosing or determining the etiology of DDs?
    a. What are the proposed advantages and disadvantages of these tests compared to standard-of-care diagnostic methods?
    b. What recommendations do clinical practice guidelines include regarding the use of the tests?
    c. Given the current evidence status, what are the implications of the tests in terms of ethics, privacy, equity, cost, or economic efficiency?
    d. What are the current evidence gaps and potential areas of future research?
    e. What ongoing clinical trials are evaluating the clinical utility of the tests?
    f. What genetic tests or testing methods under research may become clinically available for diagnosing DDs in the near future?

The scope of work for this Technical Brief is described below by the population, interventions, comparators, and outcomes of interest. This scope reflects the ECRI Institute–Penn Medicine EPC team's current thinking and incorporates the input from AHRQ, the Technical Brief's topic nominators, and the Key Informants.

Population: Children with DDs (e.g., ID and ASD) and their families (e.g., their siblings who may have the same disorder)

As previously discussed, this Technical Brief primarily focuses on patients with idiopathic or unexplained DDs, particularly GDDs, IDs or ASD. These patients have clinical manifestations but may not have shown any distinct dysmorphic or syndromic features. Several better-defined DD syndromes are also included in the brief. These syndromes include Fragile X syndrome, Rett syndrome, Angelman syndrome, Williams syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Smith-Magenis syndrome, and velocardiofacial syndrome. DDs that are typically diagnosed based upon motor or sensory impairments (e.g., cerebral palsy, hearing loss, vision impairment) or based on conventional G-banded karyotyping (e.g., aneuploidies) are beyond the scope of work.

Interventions: Genetic tests for diagnosing DDs

This Technical Brief includes only tests that are available in the United States, either as FDA-cleared or FDA-approved test kits or as an LDT provided by a CLIA-certified laboratory. We primarily focus on CMA, including aCGH and single nucleotide polymorphism (SNP) assays, because use of these tests is widespread in clinical practice and because medical genetics groups have recommended the tests for identifying genetic mutations in children with DDs.

Other types of genetic tests within the scope of work include polymerase chain reaction (PCR)-based tests (e.g., quantitative PCR), multiplex ligation-dependent probe amplification, Southern blot, sequencing, fluorescence in situ hybridization (FISH, including subtelomeric FISH), and tests used for methylation analysis, deletion/duplication analysis, and uniparental disomy study. Conventional G-banded karyotyping is beyond the scope of work.

Comparators: Standard-of-care diagnostic methods, including no genetic testing or using other clinical tests for diagnosing DDs

Clinical tests considered as comparators may vary across DDs. For example, for ASD, comparators may include Autism Behavior Checklist, Autism Diagnostic Interview-Revised, Autism Observation Scale for Infants, Checklist for Autism in Toddlers, Childhood Autism Rating Scale, Gilliam Autism Rating Scale–2nd Edition, Autism Diagnostic Observation Schedule–Generic, and Autism Diagnostic Observation Schedule–Toddler Module.[28]

For Angelman syndrome, comparators may include Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scales for Children, Stanford-Binet Intelligence Scale, Kaufman Assessment Battery for Children, McCarthy Scales of Children's Abilities, Differential Abilities Scales, Leiter International Performance (tests nonverbal abilities), Inventory for Client and Agency Planning, Scales of Independent Behavior, and Vineland Adaptive Behavior Scales.[28]

Outcomes: Patient-centered health outcomes and intermediate outcomes including changes in clinical decisions (e.g., refining treatment options, ordering other tests, referring patients to other specialists) or family reproductive decisions, diagnostic accuracy (e.g., sensitivity, specificity, positive and negative predict values) and parameters for measuring the analytic validity of a test

Relevant health outcomes may vary across different DDs. For example, for ASD, relevant health outcomes may include reduction in autism severity and improvement in language or adaptive behavior measured by a validated or standardized instrument (e.g., the Autism Diagnostic Observation Scale, the MacArthur-Bates Communicative Developmental Inventories, Vineland Adaptive Behavior Scale). Health outcomes relevant to ID include changes in cognition, remote memory, problem solving, understanding of relationships, social interaction, communication, self-care, and activities of daily living.

Methods

We describe below the methods for addressing the guiding questions previously defined.

Discussions with Key Informants (KIs)

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is/might be used, and which features may be important from a patient standpoint. KIs are particularly important for this Technical Brief, because the area of genetic testing for DDs is complex and published data for addressing some of the guiding questions are unavailable. KIs helped identify relevant data sources and contributed to a better understanding of how advanced genetic tests work, their role in clinical practice, and potential advantages or harms. KIs who worked with us for this project include clinicians who treat patients with a DD, experts on genetic testing, patient advocates, medical directors from Medicaid programs, and individuals representing professional societies. Discussions with these KIs allowed us to identify important issues from different perspectives. Office of Management and Budget clearance was not required because we limited our standardized questions to no more than nine nongovernment-associated individuals.

After AHRQ's review and approval of the completed Disclosure of Interest forms for proposed KIs, we held interviews with eight selected KIs. The interviews were held with small groups of KIs based on availability and concordance of perspectives. Each interview was summarized in writing. KIs' input was been considered as we defined the project's scope of work and prepared the draft report. Information gained from KI interviews is identified as such in the report.

Gray Literature Search

A main objective of this Technical Brief is collecting information on genetic tests for diagnosing or determining the etiology of DDs. As discussed, the majority of these tests are available as LDTs. Identifying all LDTs within the scope of this Technical Brief has been a challenge and required a multi-faceted approach, including a comprehensive search of peer-reviewed and gray literature. Based on our experience in developing an Evidence-based Practice Center horizon scan report on molecular LDTs[33] in addition to the KIs' input, we used gray literature sources, particularly the National Center for Biotechnology Information (NCBI) Genetic Testing Registry (GTR) (https://www.ncbi.nlm.nih.gov/gtr/), as the primary source for identifying tests of interest.

NCBI is a division of the National Library of Medicine at the National Institutes of Health. The NCBI's GTR is a comprehensive information source for testing offered worldwide for disorders with a genetic basis.[39] Information is voluntarily submitted by test providers. Each test is assigned a stable identifier of the format GTR000000000. GTR is designed to capture information on each test (e.g., its purpose, target populations, methods, what it measures, analytical validity, clinical validity, clinical utility, ordering information) and laboratory (e.g., location, contact information, certifications and licenses). However, the voluntarily submitted information is not equally complete for all data items. For example, data on tests' analytical validity, clinical validity, or clinical utility are often missing. When these data are indeed available, the sources of the data were rarely provided. In contrast, information on laboratories that offer genetic tests are mostly complete.

We contacted GTR to request data on genetic tests. To fulfill our request, the GTR staff used the variables we provided and delivered the data in a Microsoft Excel file. We identified tests of interest using key terms for DD conditions (including their synonyms), GTR condition identifiers, and common genes known to be related to the conditions.

We also searched two other U.S.-focused online sources—McKesson Diagnostics Exchange and GeneTests.org—to complement and confirm the information collected from GTR. McKesson Diagnostics Exchange (https://app.mckessondex.com) is an online registry of molecular diagnostic tests. GeneTests.org (www.genetests.org) is a medical genetics information resource including a directory of international laboratories offering genetic testing. Both McKesson Diagnostics Exchange and GeneTests.org are proprietary but accessible to the public. Additional gray data sources we searched include GeneReviews (www.ncbi.nlm.nih.gov/books/NBK1116/), the Association for Molecular Pathology Test Directory (www.amptestdirectory.org/index.cfm), NCBI's Online Mendelian Inheritance in Man (OMIM) database (http://omim.org/), and EuroGentest (www.eurogentest.org).

We further searched other gray literature sources, such as government and specialty society Web sites, clinical trial databases, AHRQ's Healthcare Horizon Scanning System, trade publications, and meeting abstracts to identify data addressing these tests' analytic validity, clinical validity, and clinical utility. We also searched professional societies' Web sites to identify health technology assessment reports, clinical guidelines, and consensus statements, and new tests under development.

Our search of the gray literature sources—except for the GTR—only identified a small amount of data on genetic tests. These data are less comprehensive and provide less detail than those identified from the GTR. The additional value of incorporating data from other sources to the data we collected from the GTR was deemed limited. Methods that allow us to link data from different sources also are lacking. As a result, we decided to rely only on the GTR data for this Technical Brief.

Published Literature Search

We used a variety of databases to search the peer-reviewed literature. These include Medline and Embase (Embase.com), PreMedline and PubMed in process subset (PubMed), PsycINFO (OVID) and the Cochrane library (including the Central Register of Controlled Trials, the Cochrane Database of Methodology Reviews, and the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the U.K. National Health Service Economic Evaluation Database). The National Guideline Clearinghouse (NGC) was searched for relevant clinical practice guidelines. The searches used a combination of controlled vocabulary terms and free text words and were limited to English language studies published since 2000. A detailed literature search strategy is provided in Appendix A.

Literature Review and Data Abstraction

Because of the broad scope of this Technical Brief (multiple DDs, multiple genetic tests, and various measures of test performance —analytic validity, clinical validity, and clinical utility), we screened and reviewed a large body of literature. Given the limited timeframe of this Technical Brief, a complete review of all full-text articles was not feasible. We therefore collected a portion of the data for this report from a review of abstracts. Given the nature of the data collected, this approach was sufficient for most studies. For example, the vast majority of

clinical studies were case series that reported diagnostic yield for a given genetic target or the prevalence of a given genetic aberration among specific patient populations. In such instances, key information such as the study design (i.e., case series) and the reported outcome (e.g., diagnostic yield) were identified with confidence at the abstract level. In cases where abstracts provided insufficient information, or where there was reasonable uncertainty regarding the required data, we retrieved and reviewed full-text articles.

We collected data only from studies published in English that met the inclusion criteria specified in the Scope of Work section of this document. Data collection was guided by the criteria specified on data collection forms included in the Technical Brief Protocol submitted to AHRQ for review prior to study commencement. Data review and abstraction was performed with DistillerSR®, a web-based systematic review software system (Evidence Partners, Inc., Ottawa, Ontario, Canada). Reviews of each abstract or full-text article and data extraction for each study was performed independently by two researchers. Any discrepancies between the two researchers regarding the selection or review of a given study were resolved through discussion or through arbitration led by a third researcher. Redundancies from multiple publications of the same data sets were identified and eliminated by reviewing author affiliations, study design, enrollment criteria, and enrollment dates. In such cases, the most recently published studies of these data were included in our report.

Findings

Our search of the GTR database identified 727 tests (each assigned a unique GTR identifier) within the scope of this Technical Brief. These tests are offered by 64 providers located in the United States. They are used for diagnosing, screening, or assessing the risk of DDs. All test providers, except for the United States Air Force's DNA Diagnostic Laboratory, have a CLIA certificate number. Therefore, we deem these tests to be LDTs. The test providers are located in 29 states (see Table 1).

The tables in Appendix D include detailed information about the genetic tests that we identified. The information is organized by the 11 DD categories, including ID, ASD, GDD, Angelman syndrome, fragile X syndrome, Rett syndrome, Williams syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Smith-Magenis Syndrome, and velocardiofacial Syndrome. Some tests are used for more than one DD category (e.g., used for both ID and fragile X syndrome or for both ASD and Rett Syndrome). In these cases, the tests are counted in all categories that apply. These tables include the following information for each test:

- GTR test ID
- Test provider information (name, location, lab test ID, CLIA number)
- Target chromosomal regions or genes
- Genetic method used for analysis
- Specimen source
- Whether pre- or post-test counseling is required
- Whether the test participates in any proficiency testing program

Note that all the data identified from the GTR were voluntarily reported by laboratories. NCBI established its protocol to guide the data submission process.[39] We did not independently verify, therefore do not guarantee, the data's accuracy. Independently verifying data accuracy for 727 tests was impossible within the short timeframe of this Technical Brief. Readers of this report should use caution when they interpret the data from the GTR.

Table 1, Table 2, and Table 3 are a summary of the genetic tests. As Table 1 indicates, we identified more tests for ID (or mental retardation) than for any other DD categories. Not every State has a laboratory that offers genetic tests for DDs. The impact of the laboratories' geographic distribution on genetic tests' accessibility is unclear, because patients may receive testing services from laboratories in other states. Proficiency testing ise performed for only a portion of the tests identified. The percentage of the tests for which proficiency testing is performed varies across the 11 DD categories, ranging from 22 percent for Rubinstein-Taybi syndrome to 74 percent for Prader-Willi syndrome. These PT programs include formal programs (e.g., those sponsored by the American College of Medical Genetics or College of American Pathologists) and intra-laboratory sample exchange programs.

Some laboratories offer multiple tests for the same DDs (e.g., ID, ASD). These tests differ in gene markers targeted, analysis methods used (e.g., sequencing, microarray), or the purposes of testing (e.g., screening, diagnosis). The information provided by the GTR database is not sufficient for judging whether any of these tests is the newer version of another test or why these laboratories offer multiple tests for the same DDs.

As summarized in Table 2, the common analysis methods used in these tests include comparative genomic hybridization (CGH), microarray, SNP detection, next-generation sequencing (NGS), bidirectional or unidirectional Sanger sequence analysis, multiplex ligation-dependent probe amplification (MLPA) or other polymerase chain reaction-based (PCR-based)

methods, and FISH. Some tests use more than one method (e.g., using both microarray and NGS; see tables in Appendix D). Sequencing (include both NGS and Sanger analysis) are the most frequently used methods among the tests identified. In these data tables, we use the same terminology that the GTR uses to label genetic methods. Some of these methods (e.g., microarray and CGH) potentially overlap.

Table 3 summarizes the genetic targets analyzed by the tests identified. These tests may target a single gene (e.g., *PTEN*, *FMR1*, *MEF2C*, *FOXG1*), a chromosome (e.g., chromosome 15), a chromosomal region (e.g., 15q11-q13), or the whole genome or exome (labelled as "human genome" in the GTR database). We identified more single-gene tests than multiple-gene tests. The most common targets in single-gene tests vary across DD categories (see Table 3). For the genes included in the multiple-gene tests, see tables in Appendix D.

Our search of the GRT database identified a limited amount of data on analytic validity or clinical validity for a portion of the 727 tests. However, references were rarely provided for determining where these data came from. We deemed these data to be unreliable and did not to report them in this Technical Brief.

In addition to the tests we identified from GTR, we identified one FDA-cleared commercial test kit that met the inclusion criteria for this Technical Brief. On January 17, 2014, the agency cleared Affymetrix CytoScan Dx Assay (Affymetrix, Inc., Santa Clara, California) for marketing in the United States.[40] The test's FDA-cleared indication is below:[40]

> "CytoScan Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the GeneChip System 3000Dx and analyzed by Chromosome Analysis Suite Dx Software (ChAS Dx Software).
>
> This device is not intended to be used for standalone diagnostic purposes, preimplantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations."

According to the FDA's 510(k) clearance summary document, Affymetrix CytoScan Dx Assay uses the chromosomal microarray technology and provides genome-wide coverage for the detection of chromosomal imbalances.[40] The CytoScan Dx array contains approximately 2.7 million markers which are representative of DNA sequences distributed throughout the genome. The majority of the markers (1.9 million) are non-polymorphic markers. The assay reports the copy number state (loss, gain), copy number (i.e., 0, 1, 2, 3, or 4 or greater), and position/location of chromosomal segment copy number changes across the queried genome.

Affymetrix had submitted data on CytoScan Dx Assay's performance to FDA for review. The submitted data addressed analytical performance (assay accuracy, precision/reproducibility, stability, assay controls, detection limit, analytical specificity, assay cut-off) and clinical

sensitivity/specificity. These data were summarized in the FDA's 510(k) clearance summary document.[40]

Table 1. Summary of genetic tests: availability

Condition	Number of Tests Identified	Number of Laboratories Offering the Tests	Number of States Where Laboratories are Located	States Where Laboratories are Located	Number of Tests Participating in a PT Program
Angelman syndrome	113	46	27	California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Virginia, Wisconsin	65
Autism spectrum disorders	93	23	16	California, Colorado, Connecticut, Florida, Georgia, Maryland, Massachusetts, Michigan, Nebraska, New York, Ohio, Pennsylvania, Texas, Utah, Virginia, Wisconsin	31
Fragile X syndrome	56	34	20	California, Colorado, Florida, Georgia, Iowa, Massachusetts, Michigan, Mississippi, Missouri, Montana, Nebraska, New York, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Wisconsin	30
Global developmental delay	27	18	13	California, Connecticut, Florida, Georgia, Illinois, Maryland, Massachusetts, Michigan, New York, Ohio, Texas, Utah, Virginia	17
Intellectual disability/ mental retardation	333	23	16	California, Colorado, Connecticut, Georgia, Illinois, Iowa, Massachusetts, Michigan, Nebraska, Ohio, Oklahoma, Pennsylvania, South Carolina, Texas, Utah, Wisconsin	114

Table 1. Summary of genetic tests: availability (continued)

Condition	Number of Tests Identified	Number of Laboratories Offering the Tests	Number of States Where Laboratories are Located	States Where Laboratories are Located	Number of Tests Participating in a PT Program
Prader-Willi syndrome	50	39	24	California, Florida, Georgia, Illinois, Indiana, Iowa, Massachusetts, Michigan, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Virginia, Wisconsin	37
Rett syndrome	110	25	18	California, Connecticut, Delaware, Florida, Georgia, Illinois, Massachusetts, Michigan, Mississippi, Missouri, Nebraska, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Utah, Wisconsin	62
Rubinstein-Taybi syndrome	23	8	8	California, Colorado, Georgia, Illinois, Massachusetts, Nebraska, Ohio, Texas	5
Smith-Magenis syndrome	29	19	12	California, Connecticut, Georgia, Indiana, Massachusetts, Michigan, Nebraska, Ohio, Texas, Utah, Virginia, Wisconsin	14
Velocardiofacial syndrome	78	31	19	California, Connecticut, Florida, Georgia, Illinois, Indiana, Maryland, Massachusetts, Michigan, Montana, Nebraska, New York, Ohio, Oklahoma, Pennsylvania, Texas, Utah, Virginia, Wisconsin	46
Williams syndrome	22	16	11	California, Georgia, Indiana, Massachusetts, Michigan, Nebraska, New York, Ohio, Utah, Virginia, Wisconsin	15

Source: National Center for Biotechnology Information's Genetic Testing Registry
PT=proficiency testing

Table 2. Summary of genetic tests: commonly used methods

Condition	CGH	Microarray	SNP Detection	NGS/MPS	Sanger Sequence Analysis	MLPA	PCR	FISH
Angelman syndrome	8	3	1	24	39	15	31	10
Autism spectrum disorders	11	16	7	29	30	9	6	1
Fragile X syndrome	3	3	0	7	5	0	42	0
Global developmental delay	1	13	7	7	2	0	1	0
Intellectual disability/ mental retardation	83	35	2	122	141	22	4	0
Prader-Willi syndrome	0	2	1	5	1	6	28	10
Rett syndrome	7	3	0	37	51	31	5	1
Rubinstein-Taybi syndrome	2	3	0	6	10	5	0	0
Smith-Magenis syndrome	2	3	0	12	5	0	0	6
Velocardiofacial syndrome	12	3	0	30	20	2	1	9
Williams Syndrome	0	1	0	6	0	0	0	8

Note: Some tests use more than one method.

CGH=comparative genomic hybridization; FISH=fluorescence in situ hybridization; MLPA=multiplex ligation-dependent probe amplification; NGS/MPS=next-generation sequencing/massively parallel sequencing; PCR=polymerase chain reaction; SNP=single nucleotide polymorphism

Table 3. Summary of genetic tests: genetic targets

Condition	Numbers of Single-gene Tests	Common Target of Single-Gene tests (Number of Tests)	Numbers of Tests Analyzing Multiple Genes	Numbers of Tests for Which Specific Target Genes Are Not Reported*
Angelman syndrome	67	*UBE3A* (26), *CDKL5* (14), *SNRPN* (13), *MECP2* (6)	31	19
Autism spectrum disorders	43	*PTEN* (13), *MECP2* (7), *FMR1* (3)	32	15
Fragile X syndrome	46	*FMR1* (46)	8	2
Global developmental delay	4	*CTNND2* (1), *FGFR3* (1), *FMR1* (1), *GFER* (1)	8	15
Intellectual disability/ mental retardation	215	*MEF2C* (27), *ARX* (12), *CASK* (8), *HSD17B10* (8), *FKRP* (6), *OPHN1* (6)	116	2
Prader-Willi syndrome	24	*SNRPN* (22), *PWARSN* (1), *MAGEL2* (1)	5	21
Rett syndrome	69	*MEF2C* (41), *FOXG1* (18), *CDKL5* (9)	39	1
Rubinstein-Taybi syndrome	17	*CREBBP* (12), *EP300* (5)	6	1
Smith-Magenis syndrome	7	*RAI1* (7)	12	10
Velocardiofacial Syndrome	25	*FBN1* (9)	32	20
Williams Syndrome	1	*ELN* (1)	6	15

* For these tests, no specific targeted genes are reported in the National Center for Biotechnology Information's Genetic Testing Registry database. Instead, a chromosome (e.g., chromosome 15), a chromosomal region (e.g., 15q11-q13), or "human genome" is reported as the target of analysis.

Evidence for Addressing Clinical Utility

Figure 2 summarizes the literature review workflow identifying current evidence for addressing clinical utility. Our search of peer-reviewed journals and gray literature (including manual search of journal articles' reference lists) identified 2,123 records potentially relevant to the topic of this Technical Brief. We excluded 1,694 articles based on abstract review. Most of the articles were excluded because they are not about a clinical disorder or a genetic test of interest. We were able to extract data from 307 articles at the abstract level. We retrieved 122 full-length articles because their abstracts did not provide sufficient information for data extraction or for judging whether the articles were within the scope of work. We excluded 8 articles at the full-length article level (see Figure 2 for exclusion reasons). Then, we extracted data from 114 remaining full-length articles.

Ultimately, we extracted data from 421 studies at either the abstract or full-length article level. These data include the studies' design, reported outcomes, sample size, the performance aspects it addressed (e.g., analytic validity, clinical validity, clinical utility), targeted DDs (e.g., ASD, ID, Fragile X syndrome), and testing methods used (e.g., PCR, sequencing). These data were exported from the Distiller system into an Excel file for analysis.

Table 4, Table 5, and Table 6 together provide a map of evidence that directly or indirectly addressed the clinical utility of genetic tests for DDs. Guided by the evaluation framework

previously discussed (Figure 1), we first searched for studies that directly addressed the clinical utility issues. The studies are summarized in Table 4. Our search did not identify any RCTs or non-RCT studies that directly evaluated the impact of genetic testing on health outcomes. Our search identified seven studies that evaluated the impact of testing on clinical management (e.g., medical referrals, decisions on diagnostic imaging or other laboratory testing, improvement in acquiring services) or family decisions (e.g., reproductive decisions).[22,23,41-45] We also identified three studies that evaluated the value of genetic testing perceived by families affected by DDs.[25,45,46] These studies do not provide firm evidence regarding the influence of genetic testing on health outcomes, but they help estimate the possibility of an effect. Most identified studies evaluated CMA.

Our search identified 21 studies that addressed analytic validity or clinical validity issues (Table 5). Most of the tests in these studies were not used for establishing a clinical diagnosis (e.g., ASD, ID), which is typically based on clinical evaluations using standardized measures ("phenotype-first" description of genetic disorders). Those tests were instead used to establish an "etiologic diagnosis," that is, whether a patient who had an established clinical diagnosis carried a specific genetic variant. In addition, genetic tests may be used to aid in differential diagnoses or in cases early in development when clinical diagnosis may be difficult. In a "genotype-first" approach to description of new genetic disorders, however, the etiologic diagnosis may be viewed as an early stage of defining a clinical syndrome that has not yet been well understood. Thus, a new etiologic diagnosis (i.e., the new genetic variant) is evaluated among several individuals with the genotype in common to determine whether or not they share a common phenotype. If confirmed as a new syndrome, the genotype becomes the clinical definition of the syndrome. Depending on whether etiologic diagnosis is viewed as genetic association with a clinical (phenotypic) diagnosis or as the primary diagnosis of a syndrome defined by genotype, studies that addressed testing accuracy may be interpreted as addressing either analytical validity or clinical validity. This is the reason that we summarized the studies in a single table.

The majority of the studies in Table 5 evaluated PCR or CMA. They are either case-control studies or case series. Outcome measures reported include analytic sensitivity or specificity, precision, concordance, signal-to-noise ratio, and reported range.

For this Technical Brief, we identified 132 case series that reported on the diagnostic yield of a genetic test. Diagnostic yield is calculated as the number of patients who had a "causal," "pathogenic," or "clinically significant" genetic aberration detected by the test, divided by the total number of patients tested. Although diagnostic yield indicates the percentage of patients being tested who ultimately reach a diagnosis, it does not reveal whether the diagnoses reached are correct or whether the targeted genetic aberration is truly causal, pathogenic, or clinically significant. Although improved diagnostic yield is often used by researchers as evidence to support the use of genetic tests, this improvement does not necessarily lead to improved health outcomes.

The diagnostic yield studies we identified are summarized in Table 6. These studies include those comparing diagnostic yields of two or more testing methods and those validating a new testing method. ID was the most studied DD (in 89 studies), followed by ASD (in 34 studies). CMA was the most prevalent genetic test method (in 66 studies), followed by PCR (in 36 studies).

Additionally, we identified more than 200 studies (not including single-patient or single-family case reports) that investigated any association between a genetic marker (genotype) and a DD disorder or its physical and mental characteristics (phenotype). These genotype-phenotype

association studies are exploratory in nature. They were not intended to validate a genetic test. Instead, they used genetic tests as research tools. These studies generate hypotheses and provide valuable input for developing future genotype-phenotype associations. However, it is still premature to consider the findings of these studies in building the evidence chain for addressing genetic tests' clinical utility. Therefore, we do not report these studies in this Technical Brief.

Figure 2. Literature review workflow

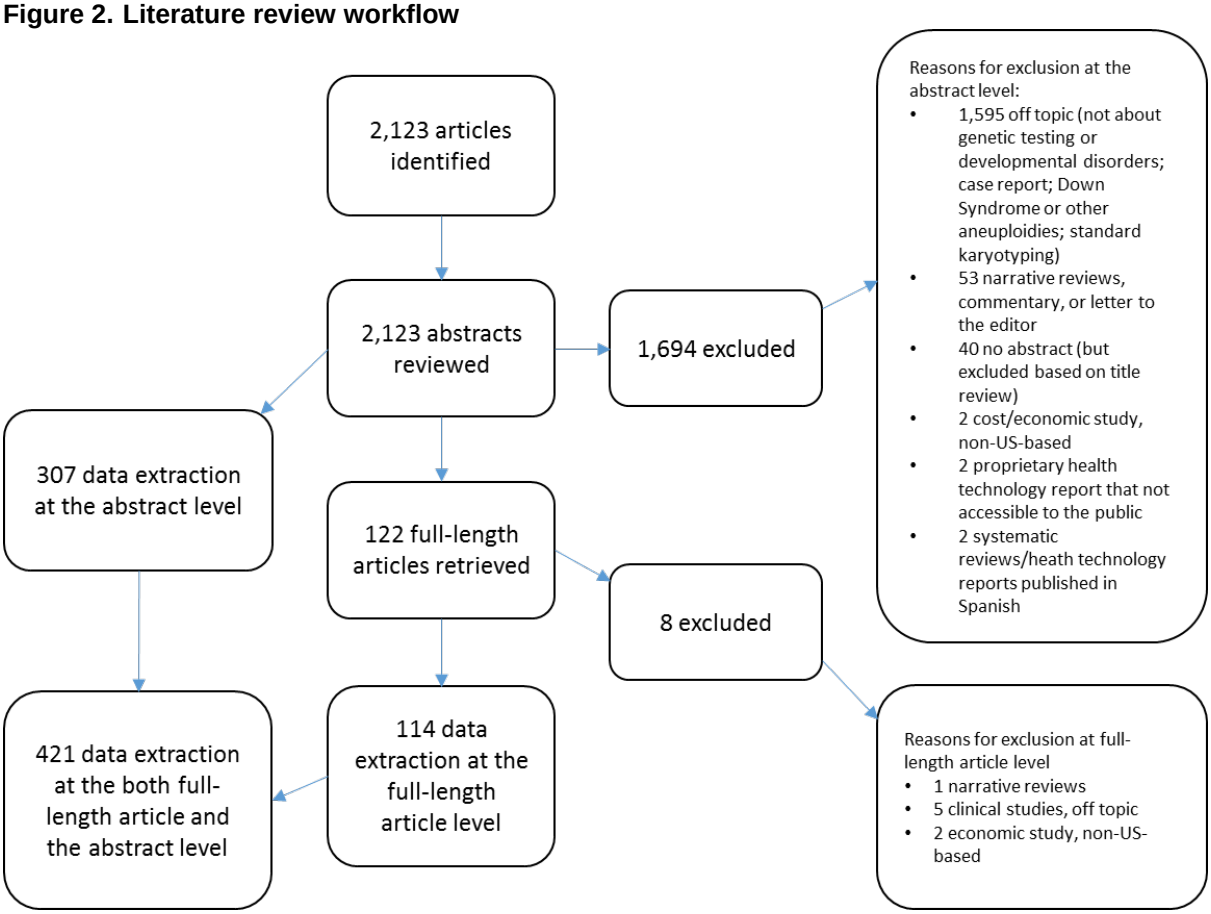


Table 4. Evidence map: clinical utility studies

Reference	DD Disorder	Test Studied	Study Design	Reported Outcomes	Sample Size
Amiet 2014[46]	ASD	CMA and FISH	Survey	Interest in the use of a genetic screening test for ASD	631
Ellison 2012[41]	Developmental delay, ID, Angelman syndrome, Smith-Magenis syndrome, Velocardiofacial syndrome, Williams syndrome	CMA	Case series	Changes in clinical management	122 (a subset of 46,298 cases)
Iglesias 2014[42]	Developmental delay, ID, ASD	Sequencing	Case series	Changes in clinical or family decisions	115
Costain 2012[45]	Velocardiofacial syndrome	Molecular diagnosis	Survey	Impact on disease understanding and certainty, on advocacy, and on opportunities to optimize medical, social and educational needs	118
Mroch 2012[22]	Developmental delay, Rett syndrome	CMA	Case series	Changes in clinical management	3
Coulter 2011[23]	Developmental delay, ID, ASD	CMA	Case series	Changes in medical care by precipitating medical referrals, diagnostic imaging, or specific laboratory testing	1,792
Bruno 2009[43]	ID	CMA	Case series	Changes in clinical or family decisions	117
Makela 2009[44]	ID	CMA	Survey	Impact on experiences acquiring services, use of support groups, the family's reproductive decisions; interest regarding the importance of an etiological diagnosis	20
Saam 2008[25]	Developmental delay, Prader-Willi syndrome, muscular dystrophy	CMA	Survey	The willingness to pay for diagnostic testing to find a genetic cause of DD from families of children with DD	48

Table 5. Evidence map: clinical validity and analytic validity studies

Reference	DD Disorder	Test Studied	Study Design	Reported Outcomes	Sample Size
Kalman 2014[47]	Rett syndrome	CMA, sequencing, PCR	Case series	Repeatability/precision	35
Inaba 2014[48]	Fragile X syndrome	PCR, methylation analysis	Case-control study	Sensitivity/specificity, Positive/negative predictive value	685
Hayes 2013[49]	Developmental delay	CMA, sequencing, FISH	Cohort study	Sensitivity/specificity	39
Stofanko 2013[50]	ID, Smith-Magenis syndrome	PCR	Case-control study	Sensitivity/specificity, Positive/negative predictive value	428
Stofanko 2013[51]	ID, ASD, Angelman syndrome, Rett syndrome, velocardiofacial syndrome, Williams syndrome	PCR	Case-control study	Sensitivity/specificity, Positive/negative predictive value	29
Koshimizu 2013[52]	ASD	Sequencing	Case-control study, case series	Sensitivity/specificity	38
Lafauci 2013[53]	Fragile X syndrome	PCR, Southern blot, biochemical assay	Case-control study	Sensitivity/specificity, ROC (AUC), repeatability/precision, reference range	215
Curtis-Cioffi 2012[54]	Fragile X syndrome	PCR, Southern blot	Cohort study	Sensitivity/specificity	78
Juusola 2012[55]	Fragile X syndrome	PCR	Case-control study	Sensitivity/specificity, repeatability/precision,	76
Lessard 2012[56]	Fragile X syndrome	Western blot	Case-control study	Sensitivity/specificity, ROC (AUC), repeatability/precision,	150
Jiao 2011[57]	ASD	A diagnostic model based on single-nucleotide polymorphisms and magnetic resonance imaging	Case-control study	Sensitivity/specificity	18
Bernardini 2010[58]	Developmental delay, ID, congenital abnormalities	CMA	Case-control study, case series	Sensitivity/specificity	70
Chen 2010[59]	Fragile X syndrome	PCR	Case series	Sensitivity	227
Filipovic-Sadic 2010[60]	Fragile X syndrome	PCR, Southern blot	Case-control study	Sensitivity/specificity, concordance	146
Coffee 2009[61]	Fragile X syndrome	PCR, Southern blot	Case-control study	Sensitivity/specificity, positive/negative predictive value	36,124
Hu 2009[62]	Fragile X syndrome	Sequencing, PCR	Case series	Sensitivity	24

Table 5. Evidence map: clinical validity and analytic validity studies (continued)

Reference	DD Disorder	Test Studied	Study Design	Reported Outcomes	Sample Size
Wang 2009[63]	Angelman syndrome, Prader-Willi syndrome	PCR and quantitative melting curve analysis	Case-control study	Ability to discriminate between deletional and non-deletional Prader-Willi and Angelman syndromes	143
Truong 2008[64]	Smith-Magenis syndrome	PCR	Case-control study	Repeatability/precision, reported range	64
Ballif 2007[65]	Developmental delay, congenital abnormalities	CMA	Case series	Repeatability/precision	6,946
Shen 2007[66]	Developmental Delay, ID, ASD, Angelman syndrome, Smith-Magenis syndrome, velocardiofacial syndrome, Williams syndrome	CMA	Case-control study	Sensitivity/specificity, repeatability/precision, concordance, signal-to-noise ratio	316
Altug-Teber 2005[67]	Angelman syndrome, Prader-Willi syndrome	CMA	Case series	Sensitivity	6

ASD=Autism spectrum disorder; ID=intellectual disability; PCR=polymerase chain reaction; ROC (AUC) =receiver operator characteristic (area under the curve)

Table 6. Case series reporting diagnostic yield

Reference	DD Disorder	Test Studied	Sample Size
Bartnik et al. 2014[68]	DD, ID, dysmorphic features; congenital anomalies	CMA	69
Bartnik et al. 2014[69]	DD, ID	CMA	256
Boggula et al. 2014[70]	DD, ID, PW, SMS, VS, WS	FISH, PCR/PCR-like	203
Byeon et al. 2014[71]	DD, ID	CMA, FISH, standard karyotyping	87
Chaudhary et al. 2014[72]	ID, FX	PCR/PCR-like, Southern blot	63
Cheon et al. 2014[73]	ID, Kabuki Syndrome	Sequencing	12
Chong et al. 2014[74]	DD, ID, ASD	CMA	105
Coutton et al. 2014[75]	ID	CMA	66
Dubourg et al. 2014[76]	SMS	PCR/PCR-like	9
Fatima et al. 2014[77]	ID, FX	PCR/PCR-like, Southern blot, Genomic DNA extracted	583
Gilissen et al. 2014[78]	ID	Sequencing	50
Helsmoortel et al. 2014[79]	ID	CMA, sequencing	10
Huguet et al. 2014[80]	ASD	Sequencing	1,578
Iglesias et al. 2014[42]	DD, ID, ASD	Sequencing	115
Kalman et al. 2014[47]	Rett	CMA, Sequencing, PCR/PCR-like	35
Lee et al. 2014[81]	RTS	Sequencing, PCR/PCR-like	16
Medina et al. 2014[82]	ID	PCR/PCR-like	119
Nicholl et al. 2014[83]	DD, ID, ASD	CMA	1,700
Palmer et al. 2014[84]	ID	CMA	67
Pereira et al. 2014[85]	DD, ID	CMA	305
Stobbe et al. 2014[86]	ASD	CMA	36
Tucker et al. 2014[87]	ID	CMA	185
Tuysuz et al. 2014[88]	PW, hypotonia	FISH, methylation analysis; karyotyping	65
Utine et al. 2014[89]	ID	CMA	100
Utine et al. 2014[90]	ID	CMA	200
Uwineza et al. 2014[91]	DD, ID	CMA	50
Vergult et al. 2014[92]	ID, congenital malformations	CMA, FISH, sequencing	50
Willemsen and Kleefstra 2014[93]	ID	Sequencing	253
Wiszniewska et al. 2014[94]	DD, ID	CMA	3,240
Ahn et al. 2013[95]	AS, PW, SMS, VS	CMA	13,412
Bahl et al. 2013[96]	ASD, Tuberous Sclerosis	PCR/PCR-like	300
Battaglia et al. 2013[97]	DD, ID, ASD	CMA	349
Behjati et al. 2013[98]	ID	PCR/PCR-like	100
Behjati et al. 2013[99]	ID	CMA, PCR/PCR-like	32
Del Carmen et al. 2013[100]	VS	FISH	268
Doherty et al. 2013[101]	DD, FX	CMA, PCR/PCR-like, Southern blot	2,046
Esposito et al. 2013[102]	DD, ID, ASD, FX, facial dysmorphism	PCR/PCR-like, Southern blot	2,750
Essop and Krause 2013[103]	ID, FX	PCR/PCR-like, Southern blot	2,690
Fan et al. 2013[104]	DD, ASD	CMA	607
Halder et al. 2013[105]	AS, PW, VS	FISH	301
Hayes et al. 2013[49]	DD, learning difficulties	CMA, FISH, Sequencing	39
Jain et al. 2013[106]	ID	CMA, karyotyping, molecular studies for FX,	101

Table 6. Case series reporting diagnostic yield (continued)

Reference	DD Disorder	Test Studied	Sample Size
Jorge et al. 2013[107]	ID, FX	PCR/PCR-like	100
Kashevarova et al. 2013[108]	DD, ID	CMA	71
Koshimizu et al. 2013[52]	ASD	Sequencing	38
Lee et al. 2013[109]	DD, ID	CMA	190
Marano et al. 2013[110]	DD, ID, ASD, seizures; dysmorphic features; hypotonia; failure to thrive	CMA	200
Mundhofir et al. 2013[111]	ID	PCR/PCR-like	436
Nicholl et al. 2013[112]	DD, ID, ASD, congenital anomalies; epilepsy	CMA	247
Pohovski et al. 2013[113]	DD, ID	PCR/PCR-like	150
Pratt et al. 2013[114]	Rett	PCR/PCR-like	12
Qiao et al. 2013[115]	DD, ID, ASD	PCR/PCR-like	82
Rodriguez-Revenga et al. 2013[116]	DD, ID	CMA, FISH, PCR/PCR-like	200
Saad et al. 2013[117]	WS	FISH	17
Shoukier et al. 2013[118]	DD, ID, congenital anomalies	CMA	342
Sorte et al. 2013[119]	ASD	CMA	50
Tos et al. 2013[120]	ID	FISH	67
Vallespin et al. 2013[121]	DD, ID, ASD	Custom whole-genome oligonucleotide-based array (called KaryoArrayv3.0; Agilent-based 8 x 60 K)	780
Vallespin et al. 2013[122]	ID, ASD, multiple congenital anomalies	FISH, custom whole-genome oligonucleotide-based array; MLPA; karyotype	120
Vergult et al. 2013[123]	ID, MCA (multiple congenital anomaly)	Sequencing	50
Vorsanova et al. 2013[124]	ID, ASD	CMA	100
Winarni et al. 2013[125]	ASD, FX	PCR/PCR-like, Southern blot, cytogenetic analysis	65
Zarate et al. 2013[126]	DD, ID, ASD, FX	CMA, FISH, PCR/PCR-like	59
Zarate et al. 2013[127]	DD, ID, ASD	X-chromosome array	59
Aradhya et al. 2012[128]	Mendelian disorders overall	CMA, Sequencing	3,018
Dos Santos Sr. and FreireMaia 2012[129]	DD, ID	FISH	15
Ellison et al. 201[241]	DD, ID, AS, PW, SMS, VS, WS	CMA	46,298
Hochstenbach et al. 2012[130]	ID	Multiplex enrichment and next-generation sequencing of the entire coding sequence of all genes	20
Iourov et al. 2012[131]	DD, ID, ASD	CMA	54
McGrew et al. 2012[132]	ASD	CMA, FX testing	395
Rafati et al. 2012[133]	ID	PCR/PCR-like	328
Rafati et al. 2012[134]	ID	FISH, PCR/PCR-like	322
Splendore et al. 2012[135]	Rett	Sequencing	139
Tos et al. 2012[136]	ID, multiple congenital anomalies	FISH, standard chromosomal analysis	24
Tzetis et al. 2012[137]	DD, ID, ASD, deafness, seizures, multiple congenital anomalies	CMA, FISH, “conventional karyotype”	334
Utine et al. 2012[138]	ID	PCR/PCR-like	100
Bremer et al. 2011[139]	ASD	CMA	223
Bruno et al. 2011[140]	DD, ID, ASD, congenital anomalies	CMA	5,000
Coulter et al. 2011[23]	DD, ID, ASD, congenital anomalies	CMA	1,792

Table 6. Case series reporting diagnostic yield (continued)

Reference	DD Disorder	Test Studied	Sample Size
Hannibal et al. 2011[141]	ID	Sequencing	110
Hayashi et al. 2011[142]	ID, multiple congenital anomalies	CMA, conventional cytogenetics	536
Rana et al. 2011[143]	ID	Multiplex ligation-dependent probe amplification technique for subtelomeric anomalies	35
Roesser 2011[144]	ASD	Karyotype, DNA for FX	507
Rooms et al. 2011[145]	ID, FX, "negative for FX"	PCR/PCR-like, MLPA	413
Shawky et al. 2011[146]	ID	FISH, routine conventional karyotyping, high resolution banding	30
Wincent et al. 2011[147]	DD	CMA	160
BahiBuisson et al. 2010[148]	Rett	PCR/PCR-like	206
Bernardini et al. 2010[58]	DD, ID, congenital anomalies	CMA	70
Dave et al. 2010[149]	ID, FX	PCR/PCR-like	720
Ezugha et al. 2010[150]	DD, ID, ASD, learning disability, hypotonia	CMA	82
Filipovic-Sadic et al. 2010[60]	FX	PCR/PCR-like, Southern blot	146
Gervasini et al. 2010[151]	DD, RTS	CMA	26
Manolakos et al. 2010[152]	DD, ID	CMA	82
Muscarella et al. 2010[153]	ASD	Sequencing, biochemical assay	862
Schaefer et al. 2010[154]	ASD	CMA	89
Shen et al. 2010[155]	ASD	CMA	933
Siggberg et al. 2010[156]	ID	CMA	150
Xiang et al. 2010[157]	ID	CMA	1,499
Auber et al. 2009[158]	DD, ID	PCR/PCR-like	296
Baris and Battaloglu 2009[159]	Rett	PCR/PCR-like	14
Bhowmik et al. 2009[160]	FX	PCR/PCR-like, biochemical assay	157
Bruno et al. 2009[43]	ID	CMA	117
Bucan et al. 2009[161]	ASD	CMA, PCR/PCR-like	4,310
Cho et al. 2009[162]	ID, AS, PW, VS, WS	FISH, PCR/PCR-like	12
Coffee et al. 2009[61]	FX	PCR/PCR-like, Southern blot	36,124
Cusco et al. 2009[163]	ASD	CMA	96
Dutta et al. 2009[164]	DD, ID, FX, congenital malformations	PCR/PCR-like, biochemical assay, cytogenetic analysis	179
Friedman et al. 2009[165]	ID	CMA	300
Gijsbers et al. 2009[166]	ID, multiple congenital anomalies	CMA	318
Giorda et al. 2009[167]	ID	CMA	2,400
Hochstenbach et al. 2009[168]	DD, ID	CMA	36,325
Hu et al. 2009[62]	FX	Sequencing, PCR/PCR-like	24
Koolen et al. 2009[169]	ID	CMA	1,364
McMullan et al. 2009[170]	ID	CMA	120
Shahdadpuri et al. 2009[171]	DD	Targeted DNA testing depending on presentation, often subtelemetric chromosome analysis	119
Utine et al. 2009[172]	ID	FISH4	130
Utine et al. 2009[173]	ID	PCR/PCR-like	65
Truong et al. 2008[64]	SMS	FISH, PCR/PCR-like	64
Ballif et al. 2007[65]	DD, congenital anomalies	CMA	6,946
Baris et al. 2007[174]	DD, ID, facial dysmorphism, other congenital anomalies	CMA	373

Table 6. Case series reporting diagnostic yield (continued)

Reference	DD Disorder	Test Studied	Sample Size
de Souza et al. 2007[175]	DD, ID, WS	FISH	18
Newman et al. 2007[176]	DD	CMA	46
Sandrin-Garci et al. 2007[177]	VS	FISH	16
Shen et al. 2007[66]	DD, ID, ASD, AS, PW, VS, WS	CMA	316
van Hagen et al. 2007[178]	WS	FISH, PCR/PCR-like	63
Rauch et al. 2006[18]	DD, ID	CMA, FISH	1,170
AltugTeber et al. 2005[67]	AS, PW	CMA	6
Coupry et al. 2004[179]	RTS	PCR/PCR-like, microsatellite analysis	22
Kleefstra et al. 2004[180]	ID, AS, PW	Sequencing, PCR/PCR-like	253

AS Angelman's syndrome (happy puppet syndrome)
ASD Autism Spectrum Disorders (autism, autism susceptibility, MRD1, 2q23.1 deletion syndrome, 2q23.1 duplication syndrome)
CMA chromosomal microarray analysis
DD Developmental delay
FISH fluorescence in situ hybridization
FX Fragile X (FMR1-Related disorders, mental retardation associated with marXq28, marker X syndrome, Martin-Bell syndrome, X-linked mental retardation and macroorchidism)
PCR polymerase chain reaction
PW Prader-Willi syndrome (Prader Labhart Willi syndrome)
Rett Rett syndrome (autism-dementia-ataxia-loss of purposeful hand use syndrome, MECP2-related disorders)
RTS Rubinstein-Taybi syndrome (broad thumb-hallux syndrome)
SMS Smith-Magenis syndrome (17p- syndrome, 17p11.2 monosomy, chromosome 17p11.2 deletion syndrome, chromosome 17p deletion syndrome, deletion 17p syndrome, partial monosomy 17p)
VS velocardiofacial syndrome (22q11.2, conotruncal anomaly, DiGeorge, Shprintzen)
WS Williams syndrome (Beuren syndrome, chromosome 7q11.23 deletion syndrome, elfin facies syndrome, supravalvar aortic stenosis syndrome, Williams-Beuren syndrome)

Studies Addressing Economic, Ethical, Social, and Legal Issues

For this Technical Brief, we searched for studies that addressed economic issues including cost-effectiveness of genetic testing for DDs. Our search did not identify any economic study conducted in the U.S. context. We identified several cost-effectiveness analyses conducted in foreign countries. We excluded these foreign studies as the findings of these studies are not applicable to the United States because of the significant differences in countries' economic and health care systems.

We did not identify any empirical study focusing on ethical or legal issues regarding genetic testing in the context of DD care. Sporadic discussions about ethical concerns (e.g., how to deal with genetic abnormalities unrelated to DD that are detected in genome-wide testing) may exist in narrative reviews and clinical studies.[31]

Clinical Guidelines

For this Technical Brief, we searched for clinical practice guidelines relevant to genetic testing for DDs that were published by medical groups or professional societies. We identified 16 relevant guidelines.[3,4,19,21,27,181-191] Table 7 is a summary of the seven guidelines that provide recommendations regarding use of genetic testing for evaluating DDs. Because genetic research and testing methods for DDs change rapidly, we did not include guidelines published beyond the most recent five years in the table. Guidelines that focus only on interpreting genetic testing results are not included in the table either. Because of the differences in their purposes and methodologies, these guidelines provide different recommendations. ASD or ID are addressed in six of the seven guidelines. CMA testing for CNV is recommended for use in evaluation of individuals with ASD, ID, GDD, or certain congenital anomalies in four guidelines.[3,19,21,27] See Table 7 for detailed recommendations.

Emerging Technologies and Ongoing Trials

The GTR data we collected did not allow an analysis to predict which type of genetic tests will be more prevalent in DD care in the future. We did not identify any data-based analysis that predicted the trend of genetic technologies for DD diagnosis or screening. However, our interview of the Key Informants suggested that the whole exome or genome sequencing may be increasingly used in the context of DD care. See Appendix B, Genetic Testing Overview, for more information on sequencing technologies.

Our search of the ClinicalTrials.gov online database identified 10 ongoing clinical trials. The purposes of these trials vary significantly. Six trials are intended to explore the genetic mechanisms or genotype-phenotype association for ASD (ClinicalTrials.gov ID: NCT01686685, NCT01749670, NCT01646866, NCT01770548) or ID (ClinicalTrials.gov ID: NCT01867554, NCT02136849). Two trials are purported to validate the algorithm (ClinicalTrials.gov ID: NCT01810341) or the sample collecting method (ClinicalTrials.gov ID: NCT01616589) used in a genetic test. Another two trials are intended to study the effectiveness of a treatment in patients selected based on genotyping findings (ClinicalTrials.gov ID: NCT00768820, NCT00859664). Eight of the 10 trials focus on ADD or ID. Seven of the 10 trials are observational cohort studies. The other three trials include two case-control studies and a nonrandomized, parallel assignment study. These trials are summarized in Appendix E.

Table 7. Summary of recent clinical guidelines

Reference	Purpose	Disorders Addressed	Recommendation Relevant to Genetic Testing
Moeschler et al. 2014[3] American Academy of Pediatrics Committee on Genetics	ID or GDD	To describe an optimal medical genetics evaluation of the child with ID or GDD. This report does not cover children with ASD who also have ID as a co-occurring disability or children with a single-domain developmental delay.	• If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test. • If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process: a. CMA should be performed in all. b. metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, guanidinoacetate /creatine metabolites. c. Fragile X testing should be performed in all. • If no diagnosis is established: a. Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high density X-CMA. Consider X-inactivation skewing in the mother of the proband. b. Female gender: complete MECP2 deletion, duplication, and sequencing study. If the specific diagnosis is certain, provide genetic counseling services by a certified genetic counselor.

Table 7. Summary of recent clinical guidelines (continued)

Schaefer et al. 2013[19] American College of Medical Genetics and Genomics	ASD	To present a tiered evaluation approach of the etiology of ASD based on current evidence to assist clinicians	• A genetic evaluation should be offered to every person with ASD. • In situations where third-party payers will cover cytogenetic studies but not CMA testing, a conventional chromosomal analysis is preferable to no cytogenetic testing at all. • Because one ASD hotspot (16p11.2) has been reported to have CNVs occurring in 0.5 to 1% of all individuals with ASDs, CMA is now recommended as a first tier test over karyotyping. • There is adequate evidence to suggest testing for Fragile X syndrome, methyl-CPG-binding protein 2 spectrum disorders, and phosphate and tensin homolog (PTEN) related conditions in patients with ASD with no other identifiable etiology. • Routine testing of females with ASD for Fragile X does not meet evidence based criteria. However serious consideration should be given to order Fragile X testing in females with ASDs when prompted by clinical parameters such as a phenotype compatible with Fragile X, a family history positive for X-linked neurodevelopmental disorders, or premature ovarian insufficiency, ataxia, or tremors in close relatives. • Given the current evidence, MECP2 testing of males with autism is not recommended. However, geneticists should be alert to the features of MECP2 duplications (drooling, recurrent respiratory infections, hypotonic facies) and consider MECP2 duplication testing in boys with autism and such features. • It is suggested that PTEN testing be reserved for patients with ASDs with a head circumference above the 98th percentile. When a family history is consistent with X linked inheritance and the patient has cognitive impairments, an X-linked intellectual disability gene panel is a consideration. • Testing for mitochondrial disorders in persons with ASDs is recommended only if supporting symptoms or laboratory abnormalities are present. • Genetic tests that have been suggested in the etiologic evaluation of ASDs but currently with insufficient evidence to recommend routine testing include: CDLK5 testing, cholesterol/7 dehydrocholesterol, Chromosome 15 methylation/UBE3A gene testing, methylation/epigenetic testing, mitochondrial gene sequencing/oligoarray, NSD1 testing, reduction-oxidation studies, purine/pyrimidine metabolism, folate-sensitive fragile sites, and selected neurometabolic screening.
Finucane et al. 2012[192] National Society of Genetic Counselors	FMR1-associated disorders	To assist genetic counselors in providing accurate risk assessment and appropriate educational and supportive counseling for individuals with positive test results and families affected by FMR1-associated disorders	No specific genetic test was recommended by this guidelines authors.

Table 7. Summary of recent clinical guidelines (continued)

National Institute for Health and Care Excellence 2011[183]	ASD	To provide information on the recognition, referral, and diagnosis of autism in children and young people from birth through 19 years of age	• Consider whether the child or young person may have medical or genetic problems and disorder (e.g., chromosome disorders, genetic abnormalities including Fragile X) as a coexisting condition and, if suspected, carry out appropriate assessments and referrals • Do not routinely perform any medical investigations as part of an autism diagnostic assessment but consider the following in individual circumstances and based on physical examination, clinical judgment and the child or young person's profile: genetic tests, as recommended by your regional genetics center, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability.
Manning et al. 2010[27] American College of Medical Genetics and Genomics	ID, ASD, GDD, or congenital anomalies	To provide guidance for healthcare providers treating patients with developmental delays, intellectual disabilities, congenital anomalies, dysmorphic features and autism spectrum disorders in determining the need for array-based genetic testing for detecting chromosomal abnormalities	• CMA testing for CNV is recommended as a first-line test in the initial postnatal evaluation of individuals with the following: o Multiple anomalies not specific to a well-delineated genetic syndrome o Apparently nonsyndromic developmental delays or intellectual disabilities o ASDs • Appropriate followup is recommended in cases of chromosome imbalance identified by CMA, to include cytogenetic/FISH studies of the patient, parental evaluation, and clinical genetic evaluation and counseling.
Miller et al. 2010[21] International Standard Cytogenomic Array Consortium	ID, ASD, or multiple congenital anomalies	To evaluate the benefits and limitations of CMA as compared to G-banded karyotyping for detecting pathogenic genomic imbalances in patients with ID, ASD, and/or multiple congenital anomalies	The authors recommended to offer CMA as the first-tier genetic test, in place of G-banded karyotype, for patients with unexplained DD/ID, ASD, or multiple congenital anomalies.
Ministry of Health, Singapore 2010[184]	ASD	To assist practitioners in Singapore who are involved in any of the following: surveillance, screening, and early identification, referral for assessment, diagnosis and intervention of children with ASD	• Children with ASD with the following features should have a genetic evaluation: microencephaly or macroencephaly, a positive family history of a genetic syndrome, dysmorphic features • Children with ASD may be offered high-resolution chromosomal studies and DNA analysis to look for an associated medical condition following diagnosis

ASD=Autism spectrum disorder; CMA= chromosomal microarray analysis; CNV= copy-number variants; GDD= global developmental delays; ID= Intellectual disability

Systematic Reviews and Technology Assessment Reports

We searched for systematic reviews and health technology assessment reports relevant to genetic testing for DD, ID, and ASD that were published by professional societies in the past five years. Our search identified three relevant documents. These systematic reviews addressed diagnostic yields of aCGH, testing for X-linked ID genes, *FMR1* testing, *MeCP2* testing, and conventional G-banded karyotyping for developmental delays, ID, or ASD. The main findings of these reviews are summarized in Table 8. We did not include systematic reviews or technology assessment reports published in non-English languages. We also excluded proprietary technology assessment reports that are not accessible by the public. Because genetic research and testing methods for DDs change rapidly, we did not search for systematic reviews or technology assessment reports published beyond the most recent five years.

Table 8. Summary of recent systematic reviews and technology assessment reports

Reference	Purpose	Resources Searched and Inclusion Criteria	Findings
Hochstenbach et al. 2011[193]	To review the contributions and limitations of genome-wide array-based identification of copy number variants (CNVs) in the clinical diagnostic evaluation of patients with mental retardation (MR) and other brain-related disorders	Publications were retrieved from the PubMed database of the National Center for Biotechnology Information. The studies were included only if (1) the clinical diagnosis was made according to international standards, (2) segmental aneuploidies detected by array-based methods was validated by an independent method, or (3) it was possible to relate the aberrations to specific patients.	In unselected MR referrals, a causative genomic gain or loss is detected in 14% to18% of cases. Usually, such CNVs arise de novo, are not found in healthy subjects, and have a major impact on the phenotype by altering the dosage of multiple genes. The expected diagnostic yield for autism spectrum disorder patients with autism is about 5% to 10% in nonsyndromic and 10% to 20% in syndromic patients. Exome sequencing in MR and autism patients revealed de novo mutations in protein coding genes in 60% and 20% of cases, respectively.
Michelson et al. 2011[20]	To systematically review the evidence concerning the diagnostic yield of genetic and metabolic evaluation of children with global developmental delay or intellectual disability (GDD/ID)	Relevant literature was reviewed, abstracted, and classified according to the 4-tiered American Academy of Neurology classification of evidence scheme	In patients with GDD/ID, microarray testing is diagnostic on average in 7.8%, G-banded karyotyping is abnormal in at least 4%, and subtelomeric fluorescence in situ hybridization is positive in 3.5%. Testing for X-linked ID genes has a yield of up to 42% in males with an appropriate family history. *FMR1* testing shows full expansion in at least 2% of patients with mild to moderate GDD/ID, and *MeCP2* testing is diagnostic in 1.5% of females with moderate to severe GDD/ID.

Table 8. Summary of recent systematic reviews and technology assessment reports (continued)

Reference	Purpose	Resources Searched and Inclusion Criteria	Findings
Sagoo et al. 2009[194]	To update a previous systematic review evaluating array-based comparative genomic hybridization (aCGH) used in patients with intellectual disability and congenital anomalies	MEDLINE, EMBASE, and Web of Science databases were searched during March 2008 with both free text and MeSH terms. No language or other search restrictions were imposed and reference lists of primary studies were checked for additional references.	The overall diagnostic yield of causal abnormalities was 10%. The overall number needed to test to identify an extra causal abnormality was 10. The overall false-positive yield of noncausal abnormalities was 7%.

Summary and Implications

Scientific advances in recent decades have led to the discovery of genetic abnormalities that may explain the reasons for many developmental disability (DD) cases. A large number of genetic tests have been developed and adopted in clinical practice. These tests are used to differentiate well-defined DD syndromes (e.g., fragile X syndrome, Rett syndrome) or, more commonly, to establish an etiologic diagnosis for unexplained intellectual disability (ID), autism spectrum disorder (ASD), or global developmental delay (GDD). For this Technical Brief, we identified 728 genetic tests for 11 DD categories using the National Center for Biotechnology Information's Genetic Testing Registry (GTR) databases. These tests employed a broad range of methods, including next-generation sequencing, Sanger sequence analysis, microarray, comparative genomic hybridization, single nucleotide polymorphism detection, multiplex ligation-dependent probe amplification, and other polymerase chain reaction–based tests. These tests analyze a single gene, a chromosome, a chromosomal region, or the whole genome or exome.

Our search identified one U.S. Food and Drug Administration (FDA)-cleared commercial test kit. All other 727 tests are laboratory-developed tests (LDTs). These LDTs are offered by 64 laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 in 29 States. Patients in some States may not have access to certain LDTs. FDA does not actively regulate LDTs at this time. However, on July 31, 2014, FDA notified Congress that it intended to publish two draft guidance documents regarding oversight of LDTs in 60 days. The proposed policy change has some significant implications for the LDTs we compiled in this Technical Brief. When the FDA guidance documents are promulgated, we will have a better chance to evaluate whether the new regulatory framework will affect any LDT's availability.

As genetic tests become increasingly available, payers have observed a quick diffusion of these tests in health care. Some tests (e.g., microarray-based comparative genomic hybridization [aCGH]) have been recommended by professional groups as first-tier diagnostic tests for DDs. The proposed benefits of genetic testing include providing an improved sense of empowerment for patient families, refining treatment options, providing prognosis, preventing comorbidities, avoiding unnecessary diagnostic tests, providing recurrence-risk-based counseling, and improving access to needed support or services. However, these proposed benefits need to be validated by clinical studies.

One major goal of this Technical Brief is to identify existing evidence for addressing the clinical utility of genetic tests for DDs. To achieve the goal, we thoroughly scanned medical literature, guided by a genetic test evaluation framework we previously developed for the Agency for Healthcare Research and Quality (see Table 10 below for a summary of this effort). We focused on evidence directly linking genetic testing to changes in health outcomes. However, our search did not identify any study—randomized or non-randomized—in that category. We consider this a major gap that needs to be filled by future research. Randomized controlled trials (RCTs) and well-designed non-randomized studies that directly compare health outcomes for use versus no use of the tests is the ideal type of study for addressing clinical utility. Conducting these studies, particularly RCTs, can be difficult for various practical reasons (e.g., long followup period, difficulty in patient recruitment, high expense). However, it is feasible to design and execute this type of study, and we feel researchers should be encouraged to make an effort in that direction.

In addition to searching clinical trials, we also searched for other types of evidence that may contribute to establishing an indirect linkage between genetic testing and health outcomes. We

identified a small number of studies assessing genetic tests' value perceived by families affected by DDs or addressing the impact of genetic testing on clinical management or family decisions. This type of study enhances our understanding of genetic tests' potential to cause changes in health outcomes (e.g., psychosocial outcomes). For example, one survey we identified reported that some parents of children with DD considered a clinical diagnosis (e.g., autism) more useful a label than a rare, specific etiological diagnosis.[44] The intensity of their need for an etiologic diagnosis was reported to diminish over time. A few case series we identified reported changes being made in patient management due to the findings of genetic tests. More studies should be performed in the future to investigate these important issues, particularly parents' views on the importance of determining etiology and how to counsel them on the value for etiologic evaluation.

Our literature search identified 21 studies addressing analytic or clinical validity issues. Most of these studies were intended to validate the performance of a newly developed test, reporting on the test's sensitivity, specificity, predictive values, concordance, or repeatability. The findings of these studies need to be further validated in future research.

We identified a large number (132) of case series that reported on the diagnostic yield of a genetic test. These case series constitute the largest portion of the evidence base we report in this Technical Brief. However, no consensus has been reached on the usefulness of diagnostic yield studies in assessing a genetic test's clinical utility (impact on health outcomes). While diagnostic yield indicates the percentage of patients being tested who ultimately reached a diagnosis, it does not confirm whether the diagnoses reached are correct. Improved diagnostic yield may not necessarily lead to a positive change in clinical management or in health outcomes.

In the context of DD care, genetic testing is often used to establish an etiologic diagnosis rather than establish a clinical diagnosis. However, researchers may not always agree on whether a genetic aberration (e.g., certain type of copy number variants) is "causal," "pathogenic," or "clinically significant." Several public databases exist to facilitate the identification of causal genetic aberrations. These databases include the National Center for Biotechnology Information, the International Standards for Cytogenomic Arrays, American College of Medical Genetics Practice Guidelines, the University of California Santa Cruz Genome Browser, the Database of Genomic Variants, and the Genoglyphix Chromosome Aberration Database. However, the existence of these databases does not completely eliminate the uncertainty in certain genetic aberrations' causal role in DDs. A more robust framework for evaluating which variants play a role in disease and are relevant to patient care is needed.[195] The uncertainty in the current databases discounts some diagnostic yield studies' validity. Ongoing efforts, such as the National Institutes of Health–funded Clinical Genome Resource (ClinGen), may provide valuable information in the future for identifying clinically relevant genetic variants.[195]

For this Technical Brief, we also searched for studies that addressed cost, ethical, legal, and social issues related to use of genetic tests for DDs. However, we did not identify any economic studies performed in the U.S. context. We did not identify any empirical research on legal, and social issues. As a result, the impact of genetic testing in those areas remains unclear.

Table 9 below summarizes the evidence gap we previously discussed. We referred to several guidance documents published by the Agency for Healthcare Research and Quality and the Cochrane Library to determine the types of evidence required for addressing a genetic test's clinical utility.[37,196,197] As the table indicates, evidence that directly or indirectly supports genetic testing's clinical utility is generally thin. Significant investment in research to fill the gap is warranted.

This Technical Brief has several limitations. First, we primarily relied on GTR to identify genetic tests. Because the GTR data were voluntarily submitted by test providers, genetic tests that were not reported to GTR are not captured by this brief. Although the GTR database is arguably one of the most comprehensive sources on genetic tests, how well the tests we identified represent the whole landscape of genetic testing for DDs is not clear. Second, within the timeframe of this Technical Brief, we were not able to independently verify the accuracy of the GTR data submitted by test providers. Although the GTR implements a solid data quality assurance program,[39] we are not certain about the program's effectiveness. Readers of this report should use caution when they interpret the GTR data we collected.

Third, DDs include a large number of disorders. This Technical Brief focused only on some common DD conditions or syndromes based on the need of key stakeholders. Genetic tests for many rare DD syndromes are not within the scope of the brief. Readers in search of that information have to seek other sources. Fourth, this Technical Brief is intended to collect basic information on genetic tests for DDs. It is not a systematic review. Although we performed a systematic search for evidence that potentially addresses genetic tests' clinical utility, we did not comprehensively evaluate the strength of evidence. To have a more in-depth understanding of how well the evidence has addressed the clinical utility issues, a series of systematic reviews may be needed.

Despite these limitations, this Technical Brief provides useful information for understanding the current landscape of genetic testing for DDs. The evidence gaps identified will help guide future research to generate the most needed evidence for addressing genetic tests' clinical utility in the context of DD care.

Table 9. Evidence gap

Domain	Ideal Evidence	Helpful Evidence	Number of Studies Identified
Clinical utility	RCTs directly evaluating if use of the test affects clinical outcomes		0
Clinical utility		Non-RCT studies directly evaluating if use of the test affects clinical outcomes	0
Clinical utility		Studies that evaluate the impact of testing on clinical management or family decisions	7
Clinical utility		Studies that evaluate patients or families' preference for genetic testing	2
Clinical utility		Diagnostic case series	132
Clinical validity	Cohort studies that evaluate the test diagnostic accuracy using a gold standard or other acceptable reference methods		0
Clinical validity		Case-control studies that evaluate the test diagnostic accuracy	0
Analytic validity	Case-control studies using appropriately validated samples to evaluate the test's analytic accuracy		16*
Analytic validity		Case series that studies analytic performance	5
Analytic validity	Studies reporting on the findings of external proficiency testing programs		0
Analytic validity	Bench-top studies that evaluate a test's repeatability, reproducibility, and other performance characteristics		0
Economic issue	Cost-effectiveness analysis		0
Economic analysis		Economic impact studies, cost reports	0
Ethical, legal, social impact	Surveys; reports of consensus-based opinions		0

*As discussed in the Findings section, some of the studies may be viewed as addressing either analytic validity or clinical validity.

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