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FOSTERING ACCESS TO NEXT-GENERATION SEQUENCING TO SHORTEN THE RARE DISEASE DIAGNOSTIC ODYSSEY

ALEXION®
AstraZeneca Rare Disease

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Next-generation sequencing (NGS) refers to large-scale DNA sequencing technology that allows for querying the entire genome (whole genome sequencing [WGS]), the exons within all known genes (whole exome sequencing [WES]), or only exons of selected genes (target panel).[1] Genome sequencing enables the potential for a precise, molecular-level diagnosis and can influence treatment and disease and reduce the financial and emotional burden that patients and their families experience in their search for an accurate diagnosis.[2] The benefits of genome sequencing in clinical settings are especially relevant for people with rare diseases who otherwise experience a "diagnostic odyssey": extensive, expensive tests and investigations at multiple clinical centers that result in an average delay in receiving a diagnosis of more than five years.[3,4,5,6] The diagnostic odyssey can be disproportionately burdensome for people with rare diseases from typically underserved communities, including people with lower incomes, people located in rural areas, and people of certain races and ethnicities.[7]

The utility of NGS is increasingly being recognized by clinical associations, which describe NGS as a first-tier test for cases where physicians are faced with a high degree of diagnostic uncertainty.[8] However, despite growing evidence of the benefits of NGS, broad uptake of NGS as a diagnostic tool for people with rare disease remains low. In this paper, we investigate the barriers to widespread access to NGS in the United States. To do so, we have reviewed academic literature, legislation, regulation, programs, and policy initiatives that impact access to NGS for people with rare disease. We evaluated federal policy and key state policies and programs primarily in California, Florida, Minnesota, Pennsylvania, and Texas. These states were in part selected because of evidence that innovative policies affecting people with rare diseases have already been implemented in these states. We identify policies that could address the barriers to accessing NGS and conclude with recommendations and opportunities for policy change.

Findings

Our review of the federal and state policy environment reveals barriers to accessing NGS faced by rare disease patients that could be addressed through policy changes to shorten the rare disease diagnostic odyssey.

There are four main findings:

1.

State governments should make access to NGS for people with rare disease a priority, starting with undiagnosed children in critical care settings

Despite clinical recognition of the value of NGS for people with rare diseases, we find that the majority of federal policies and initiatives related to NGS focus on scientific research and are not specific to rare diseases or their treatment.[9,10] State Rare Disease Advisory Councils (RDACs) generally remain in their infancy, as does the discussion of NGS as a policy or advocacy goal among councils. Nevertheless, with the expansion of research studies considering the clinical utility of NGS for children with rare disease, it is likely that WGS may play an increasing role in rare disease screening.

To support access to NGS for people with rare diseases, state RDACs could use their remit to advance state policy agendas that make NGS provision a priority. Similarly, state governments could establish precision medicine strategies or rare disease action plans that outline policy steps to expand access to NGS. Further, states could establish pilot programs that model NGS as a screening tool. State governments could establish pilot programs to support the development of cost-effectiveness and clinical-utility evidence required to implement WGS for newborn screening as a complement to current state newborn screening programs.

2.

Targeted educational materials for non-geneticist health care professionals and programs to support the availability of genetic specialists (medical geneticists and genetic counselors) can support the availability of NGS

Primary care physicians (PCPs) are typically the first point of contact for people with rare diseases and thus play a critical role in a patient's diagnostic odyssey.[11] However, several studies have shown limited experience and awareness among PCPs of the value of NGS.[12] At the same time, recent evidence points to a dearth of medical geneticists and genetic counselors, with significant variation across states.[13]

State-funded educational materials can guide physicians through ordering NGS and any related uncertainties. In parallel, a dedicated state-funded precision medicine program can lead to an increase in the number of patient referrals to NGS and can foster an expansion of the genetic specialist workforce.

3.

Broad coverage and reimbursement can support NGS availability and access to supportive care services

Despite evidence of increasing clinical uptake of NGS, coverage of NGS in state Medicaid programs varies and can be inconsistent across patient populations and care settings. For example, 27 states provide some level of coverage for WES in the outpatient setting, but only six states provide coverage of rapid WGS (rWGS) for undiagnosed, critically ill children in the intensive care unit (ICU) setting.[14,15] This patchwork of coverage policies is leading to inconsistent clinical experiences for Medicaid patients across the country. When payers do provide coverage, patient access to NGS can be limited by the implementation of utilization management tools, which can be additionally burdensome for rare disease patients and disproportionately so for patients from underserved communities.[16,17,18.] In addition, we find that reimbursement policies by care setting can lead to underutilization of NGS even when it is a covered benefit. For example, hospital provision of NGS can be disincentivized by limited payer reimbursement for NGS outside existing bundled payments. Reimbursement through diagnosis-related groups (DRGs) can impose a financial disincentive for hospitals to provide NGS, especially in critical-care settings where unexpected complications in treatment can contribute to care costs.

Coverage limitations also hinder access to genetic counselors, who can provide education and psychosocial support for people with rare diseases as they undertake NGS. Notably, Medicare coverage of genetic counselors is limited by medical necessity criteria or when ordered before starting certain medication and is not associated with NGS more generally, despite clinical recognition of the value of genetic counseling.[19,20] Furthermore, genetic counselors are not recognized by the Centers for Medicare and Medicaid Services (CMS) as health care providers, which prevents their use of telehealth with patients covered under Medicare (i.e., counselors cannot seek reimbursement through Medicare).[21,22]

State legislation could ensure broad coverage for NGS by leveraging recent, established data and evidence on the cost-effectiveness of rWGS for undiagnosed children in critical-care settings. State legislation also could prevent the excessive use of utilization management and could establish supplemental payments or health plan carve-outs to reimburse hospitals for the provision of NGS. CMS could share evidence of clinical utility and cost-effectiveness of rWGS to support consistent evaluation of NGS and encourage state Medicaid directors to align coverage bulletins. Federal legislation could require CMS's recognition of genetic counselors as health care providers and require that they be covered under Medicare.

4.

Health system capacity for genomic data storage and protection can address patient data privacy concerns and support NGS uptake

Uptake of NGS is limited by three key ethical challenges: privacy, informed consent, and return of results.[23,24] The use of electronic health records (EHRs) can exacerbate privacy concerns, despite evidence that integrating genetic data and results from NGS tests with EHRs can support the diagnosis and management of people with rare diseases.[25,26] The Genetic Information Nondiscrimination Act (GINA) of 2008 and other laws prohibit health insurers from discriminating based on the genetic information of enrollees; however, there remain limitations in the legislation.[27]

Federal legislation could require CMS to develop NGS-usage guidelines that support informed consent and patient control over data. States could fund the upgrade of health systems' genomic data-storage capacity and make it a priority by establishing precision medicine access goals, developing a long-term plan, and ensuring investment for initiatives that expand the use of NGS for rare disease diagnosis. States could leverage and expand existing genomic data protection legislation to support broader uptake of NGS, as was done in California with its expansion of GINA.[28] Overall, developing the data infrastructure to store and integrate genetic test data with EHRs and protect patient confidentiality can enable the full realization of the benefits of NGS data for rare disease diagnosis and management.

1. INTRODUCTION

We undertook this study to investigate the barriers to shortening the rare disease diagnostic journey through next-generation sequencing (NGS). Specifically, these were our objectives:

- To examine the policy barriers related to advanced diagnostic tools, with a focus on NGS
- To identify policy priorities associated with access challenges that, if addressed, create a significant opportunity to shorten the diagnostic odyssey

1.1. Shortening the diagnostic odyssey for rare disease patients

An estimated 1 in 10 Americans are affected by a rare disease. There are over 10,000 known rare diseases, over 80% of which are genetic in nature.[29,30,31] Despite advances in pharmaceutical research and development, more than 90% of rare diseases still lack an effective treatment.[32] Many rare diseases fall under the definition of "undiagnosed diseases." People with rare diseases can be defined as "not yet diagnosed" (they should be diagnosed with known diseases but have not been because they have not been referred to the appropriate clinician or had the appropriate confirmatory diagnostic test) or "undiagnosed" (diagnostic tests are not yet available for them because their diseases have not been characterized or identified).[33] Without a diagnosis, most people with rare diseases receive treatment only for their symptoms.[34] An accurate diagnosis can result in timely access to treatment and improved disease management. However, rare disease patients experience delays in diagnosis averaging five years, with some people waiting nearly a decade.[35,36,37] One reason for the delay is that traditional diagnostic techniques rely on combining specialist clinical experience from rare disease presentations with medical literature.[38] However, since rare diseases can display broad genetic heterogeneity, the clinical signs that facilitate recognition of diagnosis can be limited.[39] As a result, rare disease patients can face a lengthy "diagnostic odyssey" and often undergo extensive, expensive tests and investigations at multiple clinical centers.[40,41] Recent research by the National Organization for Rare Disorders (NORD) estimates that the average patient visits eight physicians before a diagnosis is reached.[42] Still, many patients remain undiagnosed or misdiagnosed.[43]

Over the last decade, rapid developments in diagnostics technology have enabled broad-scale, high-quality genomic profiling of patients using NGS techniques. "NGS" refers to large-scale DNA sequencing technology that allows for querying exons of selected genes (gene sequencing panels), the exons within all known genes (whole exome sequencing [WES]), or the entire genome (whole genome sequencing [WGS]).[44] Using NGS to test multiple disease genes simultaneously has paved the way for patients to receive more timely diagnosis and individualized patient therapy based on their molecular and genomic profiles.[45]

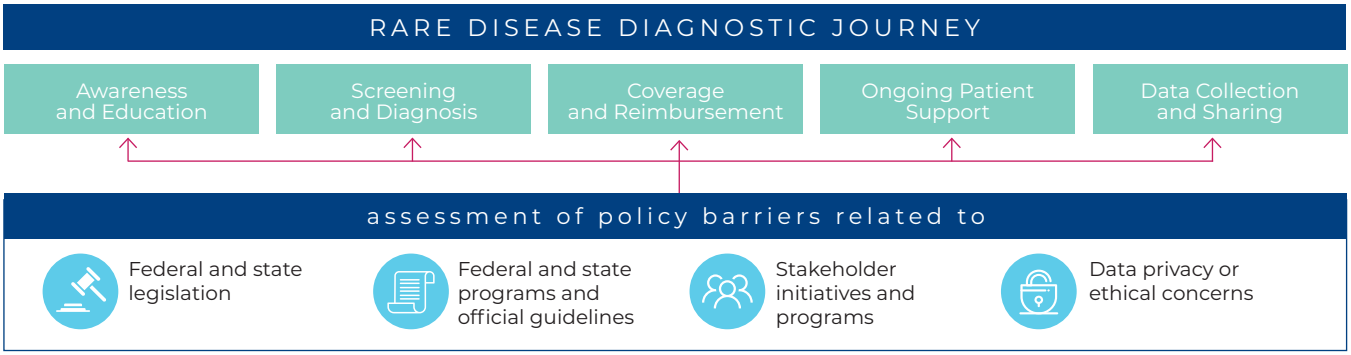
Since most rare diseases are genetic in origin, the genetic basis of NGS makes its use an increasingly integral part of diagnosis of diseases and treatment of patients.[46] Certain genetic diseases can be difficult for physicians to recognize based on clinical features alone. Therefore, the use of NGS in clinical practice can be critical for an accurate diagnosis.

1.2. Research methodology

This paper sets out the challenges and potential policy solutions to ensure broad and equitable access to NGS for people with rare diseases. We undertook a literature review focusing on state and federal official policy documents and academic research. Key policy components were identified and aligned to the rare disease patient journey as they seek an accurate diagnosis (Figure 1).

We evaluate the extent to which federal and state policies and programs enable people with rare diseases to access NGS and receive a timely diagnosis. To do so, we conducted a comprehensive search of academic literature, government legislation and reports, online newspaper articles, blogs, patient advocacy-group websites, and medical-association publications. Our search terms included "rare disease," "next-generation sequencing," "whole exome

FIGURE 1: RARE DISEASE DIAGNOSTIC JOURNEY



sequencing," "whole genome sequencing," "genomic sequencing," "legislation," "policy," and "program." To identify documents with details specific to each component of the rare disease diagnostic journey, we used additional terms related to receiving a diagnosis, such as "specialists," "coverage," "reimbursement," and "privacy concerns."

We first reviewed existing analysis of the federal policy environment and key policies and programs. Next, we identified priority states of focus based on three key criteria as of September 2022:

1. **Potential patient population impacted by policy change, proxied by the total monthly Medicaid/Children's Health Insurance Plan (CHIP) enrollment, ranked from highest to lowest in each state**[47]
2. **Evidence of innovative policies implemented to improve access to care for people with rare diseases, proxied by**
   i. Existence of Medicaid demonstration pilots providing coverage of rWGS for infants;[48]
   ii. Evidence of state legislation enforcing Recommended Uniform Screening Panel (RUSP) alignment with funding to expand state newborn screening programs to screen for additional conditions;[49] and
   iii. Legislation mandating biomarker testing coverage.[50]
3. **A geographic mix of states, e.g., including the Northeast, Southeast, Southwest, West, and Midwest**

This step enabled the identification of five states of focus: California, Florida, Minnesota, Pennsylvania, and Texas. We then conducted a search on each state. The review included approximately 150 academic studies, clinical and patient association reports, state and federal government documents, and media articles and focused on examining research published in the last 10 years. On the basis of this review, we identify policies that have been implemented at the federal and state level or that have been recommended and discussed in the policy debate. These practices form the basis of the policy recommendations in this report.

1.3. Structure of the paper

The remainder of this case study is structured as follows:

SECTION 2 provides a brief overview of types of NGS and the evidence of its value

SECTION 3 describes the challenges associated with access to NGS by rare disease patients

SECTION 4 sets out our policy recommendations to address these access barriers

2. RARE DISEASE DIAGNOSTIC APPROACHES: A BRIEF OVERVIEW

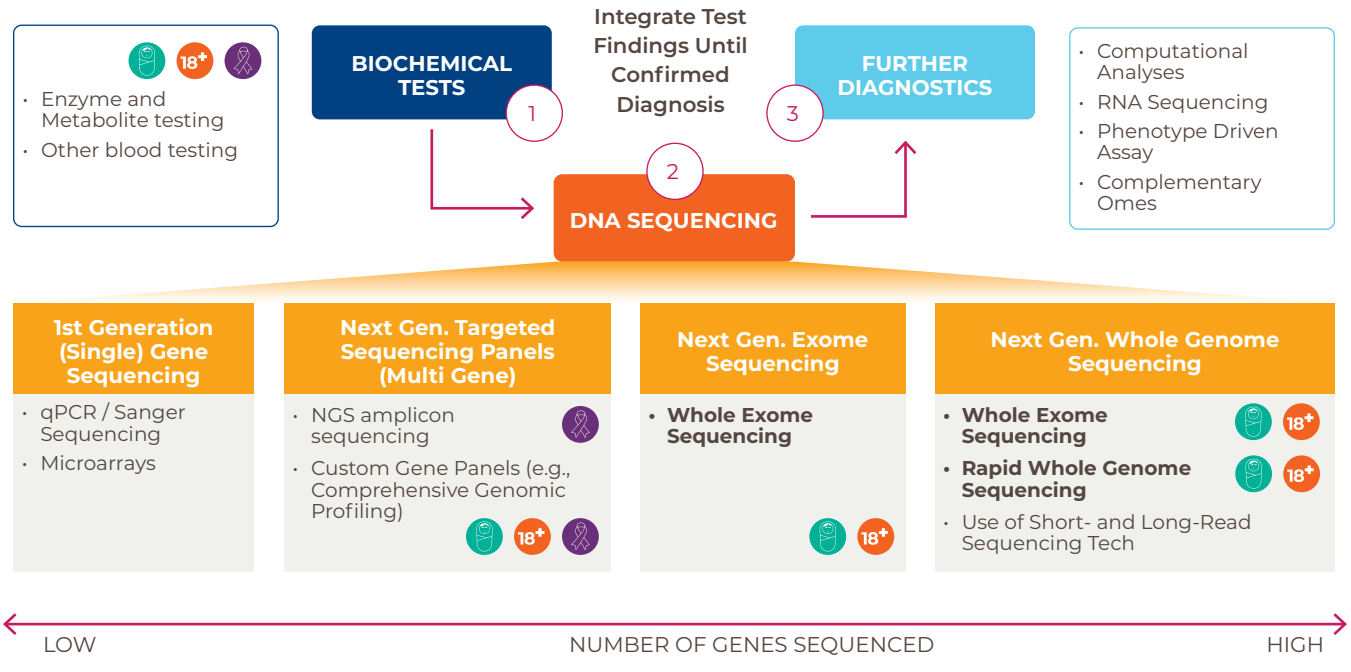
In this section we describe the types of NGS and how it currently supports rare disease diagnosis.

2.1. Types of NGS

NGS has contributed to the identification of many genes for Mendelian disorders (genetic mutations in a gene).[51] Three main sequencing approaches are used in clinical settings and are indicated for the detection of rare genetic variants in patients: **gene-sequencing panels, WES, and WGS (see Figure 2).**

- **GENE-SEQUENCING PANELS** detect known and novel variants in selected sets of genes or genomic regions.[52] Detected variants are limited to selected genes and produce a lower volume of data, lessening the workload required for interpretation. As a result, concerns related to incidental findings and identifying variants of unknown significance are lower in comparison to WES and WGS. However, due to new knowledge and gene discoveries, panels require regular updates.
- **"WES"** refers to the sequencing of 95% of the coding region of the genome.[53] WES can be interpreted with a preselected panel or with a selected set of genes relevant to a patient's phenotype. Another approach is to evaluate all rare and potentially damaging variants and compare the phenotypes associated

FIGURE 2: TAXONOMY 0F RARE DISEASE DIAGNOSTICS



KEY FOR COMMON DIAGNOSTIC APPLICATIONS:

- Pediatric Rare Disease
- Adult-Onset Rare Disease
- Oncologic Rare Disease

Source: Graphic adapted from Marwaha S., Knowles J.W., Ashley E.A. (2022) A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Medicine. 14*(1):1-22; Illumina; Azenta Life Sciences; Qin D. (2019). Next-generation sequencing and its clinical application. *Cancer Biology & Medicine.16*(1):4.

with these genes to the patient phenotype.[54] This approach enables the identification of undiscovered variants in genes. Limitations in the utility of WES are associated with the incomplete coverage of the gene and a limited ability to detect variation in genes.

- **"WGS"** refers to the sequencing of nearly the entire human genome at once.[55] WGS has the potential to discover new genes and gene modifiers, and the data obtained through genome sequencing would help to address complex inheritance models.[56] WGS can detect a broader range of genetic variation than other sequencing approaches.[57] Recent technological advances have led to the development of **rapid whole genome sequencing (rWGS)** coupled with a focused, phenotype-driven analysis of WGS data, which is capable of making a provisional molecular diagnosis in one day.[58]

WES and WGS/rWGS enable the analysis of many genes in one test, with parallel identification of incidental findings and variants of unknown significance. The advancement of technology has led to evidence that WES and WGS/rWGS are increasing in utility and cost-effectiveness compared to traditional diagnostic testing methods.[59]

2.2. The use of NGS for people with rare diseases today

Roughly half of all people affected by rare diseases are children.[60] To support early detection, presymptomatic screening at birth was introduced in the 1960s in the United States with newborn screening (NBS).[61] NBS has been implemented in the U.S. as a state public health program.[62] As a result, state NBS programs function as independent public health prevention programs, with specific associated legislation and policies. NBS programs vary across states but generally screen for a range of conditions using a small blood sample collected by a "heel prick" on the newborn's foot.[63] While NBS is considered a success by many stakeholders, variation in how genetic disorders can present and manifest in newborns can complicate diagnosis.[64,65]

Beyond screening, approaches to confirm a rare disease diagnosis have typically included multiple consultations from a range of clinical medical specialists, magnetic resonance imaging (MRI), biochemical tests, and first-generation gene-sequencing tests such as Sanger sequencing, which relies on evaluating a single gene fragment at a time.[66] Although these technologies have enabled the diagnosis of many rare diseases and treatment of many patients, the diagnostic yields are low and often dependent on what patient and potential disease information (e.g., patient physical characteristics at presentation and physician clinical knowledge) is known when the test is conducted. As a result, a large proportion of patients remain undiagnosed.[67,68]

More recently, NGS has garnered broad acceptance as a diagnostic tool for rare diseases.[69] While data illustrating NGS uptake by state are unavailable, literature highlights particular recognition of NGS as a first-tier test in diagnostics within neonatal intensive care units (NICUs) for children who are suspected of having a genetic disease.[70] NICUs are especially relevant to support the clinical uptake of innovative rare disease diagnosis methods since genetic disorders are the leading reason for hospitalization and mortality caused by congenital malformations, deformations, and chromosomal abnormalities.[71]

In addition, rWGS's use as a complement to current state NBS programs is increasingly the subject of research. For example, recent research has acknowledged that NBS programs have not kept pace with genomic innovation, but there is significant potential for improved newborn screening and diagnosis of rare disease through NGS in conjunction with conventional NBS methods.[72,73] Despite research findings that suggest the clinical utility of NBS by rWGS, its cost-effectiveness and practical implementation have yet to be tested at a national scale. Further, to date, most people with rare diseases who have undergone NGS were tested through research protocols rather than standard clinical practice.[74] This suggests a disparity between clinical value recognition and clinical adoption of NGS for people with rare disease.[75]

2.3. The value of NGS for rare disease patients

Precise, molecular-level diagnosis through genome sequencing can influence medical management and reduce the financial and emotional burden that patients and their families experience in their search for an accurate

diagnosis.[76] The utility of NGS is increasingly being recognized by clinical associations, which note NGS as a first-tier test for cases where physicians are faced with a high degree of diagnostic uncertainty.[77] Clinical associations and physician groups have established recommendations for use, such as the following:

- **The International Rare Diseases Research Consortium Solving the Unsolved Task Force** recommends exome or genome sequencing as first-line tests for people with syndromes without a name, which are not recognizable as described disorders.[78]
- **The American College of Medical Genetics** has published guidelines on the use of WES and WGS in clinical practice for specific populations.[79,80,81]
- **The American Society of Clinical Oncology (ASCO)** recommends that patients with metastatic or advanced cancer undergo genomic sequencing in cases where the results can be used as biomarkers to guide the use or exclusion of certain treatments for their disease.[82]

Despite growing evidence of the benefits of NGS as a first-tier test for rare disease populations, broad uptake of NGS remains slow. As of March 2023, only six U.S states have Medicaid coverage policies on rWGS.[83] In the next chapter, we investigate the barriers to widespread access to NGS for people with rare disease in the U.S.

3. KEY CHALLENGES TO ACCESS TO NGS FOR RARE DISEASE PATIENTS

Drawing on the academic literature, four key barriers limiting access to NGS by people with rare diseases have been identified:

1. Low prioritization of access to NGS for people with rare diseases
2. Gaps in non-geneticist preparedness to provide NGS and disparities in genetic specialist availability
3. Variation in payer coverage of, and reimbursement for NGS
4. Limited protection of patient data privacy

3.1. Low prioritization of access to NGS for people with rare diseases

Despite clinical recognition of the value of NGS for people with rare diseases, we find that policies to support access to NGS for people with rare disease in clinical settings are limited.[84,85] For example, the majority of federal policies and initiatives related to ensuring access to NGS focus on scientific research or on specific cancers and are not specific to rare diseases.[86,87] One exception is the Ending the Diagnostic Odyssey Act of 2021, which was introduced to provide federal support for the use of WGS for certain undiagnosed children under the Medicaid program.[88] The bill would have created a pilot program to cover 75% of the costs of a child's rWGS through Medicaid for the first three years, incentivizing states to cover the remaining 25%. As of December 2022, the bill did not advance in the U.S. Senate and will need to be reintroduced in a new session of Congress. The result is that few policies support access to NGS for people with rare diseases.

To highlight the unique challenges facing rare disease patients, 27 states have established Rare Disease Advisory Councils (RDACs), which aim to coordinate research on rare disease treatment, enhance access to services, drive policy and advocacy efforts, and support community

awareness.[89,90] RDACs are composed of a diverse set of stakeholders in the rare disease community, including health care professionals, researchers, politicians, and patient advocates.[91] RDACs like the one in Minnesota are examining the diagnostic odyssey through methods such as surveys of the rare disease community.[92] The objective of such surveys is to identify the barriers to timely diagnosis. However, despite the growing prevalence of RDACs and their objective of making rare disease policy issues a priority, discussion of NGS as a policy or advocacy goal among councils has been limited.

3.2. Gaps in non-geneticist preparedness to provide NGS and disparities in genetic specialist availability

Primary care physicians (PCPs) are typically the first point of contact for people with rare diseases and thus play a critical role in a patient's diagnostic odyssey. However, several studies have shown limited experience and awareness among PCPs of the value of NGS.[94,95] For example, a study surveying physician awareness and utilization of genetic services in Texas found that only half of respondents were aware of genetic services in their area, and over two-thirds never or rarely referred patients to genetic counselors or other genetic specialists.[96] Separate evidence from a survey in Arizona highlights that physicians with limited or no training in genetics are less likely to order a genetic test for any purpose, while two-fifths (41%) of physicians noted that their lack of training identifying appropriate genetic tests and interpreting testing results was the most significant barrier to recommending genetic testing for their patient.[97] Given that some current access requirements, including those of Michigan Medicaid, require that a treating physician or medical geneticist order NGS tests, non-geneticists' active involvement and knowledge of genetic testing is essential to reduce access barriers and encourage greater use of advanced diagnostic tests.[98,99]

Clinical guidelines can recommend genetic testing to confirm the diagnosis of specific rare conditions and cancer indications. Guidelines published by organizations such as the National Society of Genetic Counselors, the American Cancer Society, and ASCO support referral for genetic assessment in specific cases.[100,101] NORD provides physician guides to support clinicians and facilitate early diagnosis.[102] However, we find no evidence of state or federal guidelines to support NGS awareness among PCPs. Despite clinical guidance regarding NGS, evidence suggests that insufficient clinical criteria, errors in clinical judgment, and implicit physician bias about certain patient groups remain barriers to timely rare disease diagnoses.[103,104] Furthermore, as discussed later in this document, insurers' criteria for coverage of genetic testing are often unclear, and they vary across plan type.[105,106] Uncertainty about the likelihood of coverage influences physicians' perception of affordability for patients and their willingness to order a test: studies have shown physician prescribing behaviors change depending on patient insurance status and type.[107]

Further, there is significant evidence of the negative views of NGS and genetic testing that Blacks, Hispanics/Latinos, and members of other historically underserved groups may hold, given their concerns about racial discrimination and their mistrust of the health care system.[108] However, recent studies also report that Blacks are eager to receive genetic testing once they are made aware of the indications for it and its implications.[109] Research highlights the need for educational materials to advance the cultural competency of physicians and to ensure that recommendations for NGS of racially and ethnically diverse patients are provided in a sensitive and effective way that addresses both group differences and individual needs and preferences.[110]

3.2.1. Disparities in access to medical genetic specialists

Many payers' NGS coverage policies require referral by a medical geneticist.[111] Medical geneticists are physicians who have received specialized training in medical genetics; they evaluate, diagnose, and treat people who present with genetic indications or specific genetic conditions, so they are likely to have a deep understanding of NGS's utility.[112] However, we find evidence of disparities in patient access to genetic specialists. For example, as of April 2020, there were approximately 1,240 medical

geneticists nationally, roughly two per 500,000 people.[113] The availability of genetic specialists varies greatly state by state; only two states average more than four medical geneticists per 500,000 people, while 11 states average less than one genetic specialist per 500,000.[114] Geographical disparities in the availability of geneticists who can support rare disease diagnosis through NGS can lead to inequitable patient access to timely diagnosis.

3.3. Variation in payer coverage and reimbursement for NGS

Despite evidence of increasing clinical uptake of NGS, only a few state Medicaid programs cover WGS for use as a diagnostic tool.[115,116] We find that all five states whose policies we reviewed (see Table 1) have Medicaid coverage of gene-sequencing panels for specific genetic markers as well as for patients meeting the criteria for medical exceptions with physician attestation. Four of the five states reviewed cover WES in a limited way through certain criteria, typically requiring patients to have unknown conditions with suspected genetic origins that gene-sequencing panels could not address. As of March 2023, two of the states reviewed cover rWGS for infants under the age of one who are admitted to the intensive care unit with undiagnosed conditions that have suspected genetic origins.

TABLE 1: SUMMARY OF MEDICAID COVERAGE OF SELECT NGS TESTS (as of March 2023)

State	Medicaid Coverage of Next-generation Sequencing		
	Gene-sequencing panels	WES	WGS
California[117]	✓	✓	✓*
Minnesota[118]	✓	✓	✓*
Florida[119]	✓	✓	✗
Pennsylvania[120]	✓	✓	✗
Texas[121]	✓	✗	✗

* California and Minnesota Medicaid plans cover rWGS for all infants under one year of age in the ICU with unknown conditions.

KEY:

✓ Limited Coverage (prior authorization, coverage of specific mutations only, coverage for specific demographics)

✗ Not Covered

At the federal level, the Ending Diagnostic Odyssey Act of 2021 (S. 2022), which would encourage state Medicaid programs to cover WGS for youth under the age of 21 by matching 75% of the testing costs for the first three years, did not progress beyond the U.S. Senate Finance Committee in the 117th Congress.[122]

In addition, we find evidence of inconsistent coverage policies across state Medicaid plans, which lead to different criteria for coverage, such as the following:[123]

- Payers requiring NGS to be ordered by the infant's physician only after evaluation by a medical geneticist, such as under Minnesota's state Medicaid program[124]
- Payers deeming NGS to be "experimental or investigational" and therefore not covering the tests, as in California[125]

At the federal level, in 2018, Medicare issued a National Coverage Determination (NCD) to cover NGS for beneficiaries with advanced or metastatic cancer and no previous NGS.[126] The varying coverage criteria are likely associated with differences in payer evidence requirements. Studies highlight that plan policy variations emerge from the range of factors used to influence coverage policies, including the type of cited evidence and perception of the evidence.[127] Specifically, negative coverage policies cited fewer and older references compared to positive coverage policies.[128] One emerging trend to support broad access to NGS has been real-world evidence data collection through state Medicaid pilot programs. These short-term programs provide the opportunity to demonstrate the value of innovative diagnostic approaches for certain populations through data collection.[129] California, Florida, and Michigan implemented pilot programs (Projects Baby Bear, Baby Manatee, and

Baby Deer, respectively) that covered rWGS for high-risk infants in 2018–2020.[130] Project Baby Bear in California, the first pilot funded by state legislation (the Budget Act of 2022 [S.B. 840]), found that rWGS with a three-day turnaround led to the diagnosis for 40% of the sample of 184 critically ill infants. A further 32% of infants participating in the pilot received a change of care as a result of their diagnosis.[131] State legislators took notice and subsequently signed Assembly Bill No. 133 into law on July 27, 2021, ensuring rWGS access by any Medi-Cal beneficiary who is one year of age or younger and receiving hospital services at an intensive care unit.[132,133] Michigan hospitals undertook their own pilot, Project Baby Deer, to provide access to rWGS in 2021.[134] In 2023, the Florida governor signed into law a state budget that provides coverage of rWGS, building on the work from its pilot program.[135] Florida's Project Baby Manatee, which differed from the California and Michigan pilots in that it included participants from the Pediatric Intensive Care Unit at Niklaus Children's Hospital, found that rWGS was associated with 40% of pilot participants receiving a genetic diagnosis.[136] Florida's pilot program results indicate the utility of rWGS in shortening the diagnostic odyssey for populations with a wider age range than those examined in California and Michigan.[137]

Payers require evidence of clinical utility and cost-effectiveness to inform coverage decisions. State-funded pilot programs in California, Florida, and Michigan demonstrated that rWGS of ICU-admitted infants less than one year old with unknown conditions led to diagnosis rates of 35%–43%, changes in care decisions for 27%–38% of patients, and net per-patient cost savings ranging from $2,842 to $75,307.[138,139,140] These outcomes led to coverage expansions for rWGS in this population by Medicaid in California through legislation and in Michigan through a state agency policy change, as well as by Blue Cross Blue Shield (BCBS) plans in eight states and for federal employees.[141,142,143]

While state pilot programs to date have focused on NGS in infants and children, there is emerging evidence that NGS can be integrated into routine preventive care. While not specific to rare diseases, broad population access to NGS can bypass the restrictions associated with specific specialist referral and can be provided to adult patients.[144] In Pennsylvania, the Geisinger health system, a private, payer-provider integrated health system covering much of central and northeastern Pennsylvania, implemented an opt-in WES screening called MyCode at no cost for all patients covered by the system. The aim is to detect clinically meaningful aberrant genes for a growing list of rare diseases and cancer.[145, 146] MyCode screens for 76 genes associated with 27 conditions. While MyCode is focused on the provision of WES in the outpatient setting, its adoption signals a willingness to integrate NGS into health care more broadly.

3.3.1. Coverage limitations

When payers do provide coverage, patient access to NGS can be limited by clinically inappropriate utilization management.[147,148,149] The burden of utilization management can disproportionately fall on patients with a complex diagnosis, such as a rare disease, by compounding delays and complicating access to care, and there is growing evidence of the uneven burden of utilization on Asian, Black, and Hispanic patients.[150,151] We find evidence that over time, payers have gradually expanded coverage of previously excluded advanced diagnostic technologies, including WES and tumor sequencing, as their clinical value becomes widely demonstrated and adopted into clinical guidelines.[152,153,154] Coverage expansion timelines and levels of management vary among payers.[155,156]

Even when NGS tests are included among covered benefits, excessive utilization management, including prior authorization requirements, leads to variations in coverage and payer denials of medically necessary tests. Around 30% of prior authorization requests to private payers were denied compared to 15% of requests to Medicaid/CHIP payers, as identified by a retrospective claims analysis of prior authorization requests for genetic testing at two academic children's hospitals in Texas between 2017 and 2018.[157] Diagnostic test types in the study included exome sequencing and cytogenetic (chromosomal microarrays), epigenetic, mitochondrial, and single gene/multigene panels.

In other words, privately insured children in Texas were twice as likely as publicly insured children to be denied genetic testing, suggesting that payer type can limit access to potentially medically necessary testing. Denial rates were even higher for exome sequencing (private payers: 37%; public payers: 28%) and gene panels (private payers: 39%; public payers: 24%), both of which had relatively high diagnostic yields of 31% and 30%, respectively, compared to other genetic tests. Over half of denials were due to payers determining that the testing requests were not medically necessary or essential for medical management (31%) or that they were experimental or investigational (24%). These justifications suggest that payer perceptions of test utility are a barrier to patient access and could be shifted with clinical evidence and guidelines.

In addition, we find evidence that payers' coverage policies lag behind medical societies' clinical recommendations regarding NGS. For example, payers have incrementally expanded coverage for biomarker testing for specific genes or gene panels, resulting in a delay as compared to clinical best practices.[158,159] In a 2021 review of multigene panel coverage among the largest commercial insurance plans in each state across four tumor types, 71% were more restrictive than National Comprehensive Cancer Network guidelines, among which 52% restricted panel size and 63% restricted use by tumor type.[160] Because an estimated 80% of the thousands of known rare diseases have genetic origins, this trend of gene-by-gene coverage expansion prevents patients with rare diseases from receiving necessary biomarker testing as genetic biomarkers are identified. States have had mixed success when trying to address this gap with legislation.[161] Legislation requiring state Medicaid programs to provide coverage for medically necessary and scientifically justified biomarker testing, including for WGS, has been enacted in Arizona, Illinois, Louisiana, and Rhode Island.[162] In California, however, the Biomarker Testing bill (S.B. 912) passed both the state Senate and Assembly but was vetoed by the Governor.[163] Without coverage, patients must rely on out-of-pocket funds or seek nontraditional funding (e.g., research grants, patient groups, hospital charitable care) to cover the costs of advanced diagnostic testing.[164]

3.3.2. Insufficient payer reimbursement of NGS

Even when payer coverage exists, we find that reimbursement for NGS is not always sufficient to offer the incentive for providers to order tests. We find that hospital provision of NGS can be disincentivized by gaps in payer reimbursement of NGS. For example, California's Medi-Cal currently reimburses providers through standard inpatient diagnosis-related group (DRG) billing, which are fixed, bundled payments to the hospital for inpatient services. Payment is provided based on a DRG code describing the episode of care.[165] However, hospital revenues are under pressure if costs per episode of care for a patient are greater than the associated DRG rate, which they often are in cases involving children in the ICU, given the potential for unexpected care complications. Therefore, reimbursement of NGS through DRGs may expose hospitals to financial risk and disincentivize physicians from recommending NGS to patients.

3.3.3. Barriers to genetic counselor access for patients and caregivers

We find that people with rare diseases and their caregivers face significant psychosocial challenges throughout the diagnostic odyssey. As described earlier, people with rare diseases often undergo multiple clinical tests and see a range of specialists as they seek a diagnosis. The lack of care coordination can negatively impact patients' and caregivers' physical health, finances (through lost earnings and travel), school and work engagement, and emotional well-being.[166] In addition, patients and caregivers face unique emotional challenges when they receive NGS results. For example, patients can feel overwhelmed by the complexity and implications of genetic test results, be concerned about informing relatives who may share genetic risks, and face ethical issues associated with privacy and data sharing.[167]

Medical recognition of the need to support patients with the emotional burden and nonclinical costs of the rare disease diagnosis odyssey is growing: the American College of Medical Genetics and Genomics recommends that WGS and WES be accompanied by consultation with a genetics professional and adequate pre- and post-test genetic counseling.[168]

Genetic counselors are health care professionals with training in medical genetics who work with people affected by genetic disorders.[169] They educate patients about the testing process and support patient navigation throughout the process.[170] The involvement of a genetic counselor as an educational resource alongside a medical geneticist's clinical advisement to test can support a patient's positive experience when undergoing NGS. Genetic counseling involves educational and psychosocial support for people to help them understand the medical, psychological, and familial aspects of the genetic elements of their diagnosis, which is especially important for people with rare diseases.[171,172] Evaluations of the economic impact of using genomic sequencing to diagnose rare diseases have demonstrated that parents find genetic counselors to be a valuable resource who facilitate complex decisions.[173] Other studies have demonstrated the cost-effectiveness of providing genetic counseling.[174]

However, access to genetic counselors is hindered by availability and coverage limitations. As of 2019, there were 4,700 across the country, roughly seven per 500,000 people, indicating a lack of availability and accessibility of genetic counselors.[175] In addition, genetic counselors are not currently recognized by CMS as health care providers.[176] Instead, Medicare coverage of genetic counselors under CMS is limited by criteria associated with medical necessity or certain medication initiation and is not associated with general NGS availability.[177] Legislation introduced in 2019 (H.R. 3235, Access to Genetic Counselor Services Act) proposed Medicare Part B coverage of genetic counselors and their associated services beyond those select situations, but it failed to pass in the 117th Congress.[178] Further, not all commercial payers cover genetic counseling services.[179]

An additional implication of the lack of CMS recognition of genetic counselors as health care providers is its effect on telehealth use. Telehealth has the potential to make NGS more accessible for people with rare diseases in rural and underserved areas.[180] Given the lack of CMS recognition, genetic counselors' use of telehealth with patients is not covered under Medicare (i.e., counselors cannot seek reimbursement through Medicare).[181] The current challenges of state-specific licensure are exacerbated for telehealth providers because they can potentially engage in more interstate services than in-person providers.[182] Coverage legislation has not moved through Congress in recent years, despite evidence that coverage of genetic counselors could further support the availability and accessibility to NGS.

3.4. Limited protection of patient data privacy

NGS has the potential to shorten the rare disease diagnostic odyssey, which can be disproportionately lengthy, costly, and burdensome for underserved populations. Further, genomic sequencing for children has been demonstrated to alleviate parental guilt and lead to inclusive decision-making for future care, particularly among underserved families.[183] However, uptake of NGS is limited by three key ethical challenges: privacy, informed consent, and return of results.[184,185] Privacy and confidentiality are inherent in medical practice, and NGS-specific issues include the potential for patient reidentification and the implications of privacy breaches in the context of the information that can be inferred from an individual's genome about the patient and their relatives.[186] The Genetic Information Nondiscrimination Act (GINA) of 2008 and other laws prohibit health insurers from discrimination based on the genetic information of enrollees; however, limitations remain.[187] For example, the law does not protect against genetic discrimination by disability insurance or long-term care insurance carriers, and the law does not apply if the individual has a positive genetic test and overt disease symptoms. As a result, research has found that people are likely to decline genetic testing due to concerns about results being used to determine eligibility for employment and insurance coverage.[188]

Several studies have demonstrated that rare disease patients are willing to share data, even if the results benefit only future generations.[189,190] This indicates the importance of leveraging policy and legislation to empower patients to make informed decisions about obtaining a diagnosis though NGS and data sharing to support future research. Research has demonstrated that offering people more direct control over their genomic data can help to reduce concerns about privacy and discriminatory practices.[191]

4. POLICY RECOMMENDATIONS TO SHORTEN THE RARE DISEASE DIAGNOSTIC ODYSSEY

This paper explored the key NGS access challenges experienced by people with rare diseases and identified the associated opportunities for policy change. The policy opportunities suggested in this report are based on policies and programs that have been implemented at the federal and state level or recommended and discussed in policy debates. If adopted, these recommendations for change have the potential to improve access to NGS and will be a starting point for policy changes that can shorten the rare disease diagnostic odyssey and improve access to timely treatment:

1. State governments could make access to NGS for people with rare disease a priority, starting with undiagnosed children in critical care settings

Current policy efforts fail to make the unmet needs of people with rare diseases a priority, despite significant scientific evidence demonstrating the utility of NGS for rare disease diagnosis. To improve the political prioritization of access to next-generation diagnostic tools for people with rare diseases, state RDACs could use their remit to shape state policy agendas. The Minnesota RDAC exemplifies this approach by examining the diagnostic odyssey with a view toward informing policy.[192,193]

Beyond RDACs, California has used a state action plan to make the use of NGS a priority, though it does not specifically target rare disease patients. For example, the California Precision Medicine Advisory Committee, part of the broader California Initiative to Advance Precision Medicine, is a public-private technical advisory group established in 2015 by the state with associated state funding.[194] The Committee produced an action plan report for California's governor that included policy recommendations to encourage the use of NGS and precision medicine.[195] The overall focus on precision medicine and NGS in California could be associated with Blue Shield of California becoming the first health plan in the U.S. to cover rapid and ultra-rapid WGS to help diagnose critically ill babies and children in intensive care with unexplained medical conditions, which in turn helps these children receive precision care.[196]

Further, with the expansion of research studies considering the clinical utility of NGS for children with rare disease, it is likely that WGS may play an increasing role in state NBS programs.[197] To complement the policies that support access to WGS for undiagnosed children in critical-care conditions, states could establish pilot programs that model the potential of WGS as a rare disease screening tool. Pilot programs like those in California, Florida, and Michigan can support the development of cost-effectiveness and clinical utility evidence required to implement WGS for newborn screening as a complement to current state NBS programs.

POLICY RECOMMENDATION —

- **To support the availability of NGS, state RDACs could advance rare disease state policy agendas that make access to NGS a priority.**
- **State governments could establish state precision medicine strategies or state rare disease action plans that outline policy steps to expand access to NGS. A starting point could be to make access to rWGS for undiagnosed children in critical-care settings a priority.**
- **State governments could establish pilot programs that model the potential of WGS as a newborn screening tool, as a complement to the use of WGS for undiagnosed children in critical-care conditions and current state NBS programs.**

2. Targeted education materials for non-geneticist health care professionals and programs to support the accessibility of genetic specialists (medical geneticists and genetic counselors) can support the availability of NGS

The lack of educational support for non-geneticist physicians and the misalignment between clinical guidelines and payer coverage requirements are barriers to recommending NGS for people with known or suspected rare diseases. Continued education, more informational materials, and guidelines and toolkits can support PCPs and non-medical geneticists to help them align with growing evidence and medical societies' recommendations on the utility of NGS.[198,199,200] Tailored, state-funded information and educational materials to support physician access to NGS has been demonstrated to lead to improved physician confidence in their skills to implement NGS.[201]

Further, educational support for non-geneticist physicians should aim to address the potential negative views of NGS that people from minority and other historically underserved groups may hold. Research has highlighted that PCP education materials should include communication strategies for patients who experience literacy, language, cultural, and other social barriers and inequities to ensure engagement with people living with rare diseases who are from typically underserved populations, including people with lower incomes, people located in rural areas, and people of certain races and ethnicities.[202,203]

The potential to expand the equitable accessibility of health care professionals with specialist genetic knowledge has been demonstrated by dedicated provider programs. For example, Sanford Health, the largest nonprofit rural health care system in the U.S., pioneered a health system–wide, precision medicine program to expand the role of genetic testing in all aspects of care.[204] The multidisciplinary program prioritized educational sessions and clinic presentations designed by genetic specialists. The program led to a fivefold increase in referrals to medical geneticists as well as a threefold increase in the number of full-time-equivalent medical geneticists and genetic counselors from 2013 to 2020, likely reflecting the impact of educational efforts to make providers more aware of their access to genetic specialists.

Further, an interim step to increase access to genetic specialists would be for states to support the licensing of medical geneticists and the development of interstate compacts, which could enable greater access to specialist care for rare disease patients.[205] Licensing programs and interstate compacts also can be used to support the development of other medical specialists who are involved in the provision of NGS with a focus on rare diseases.

Finally, studies have demonstrated that multidisciplinary specialist teams can support the availability of NGS for people with rare diseases.[206,207] Integration of NGS within the health care delivery system can be driven by regional genetic service support models, which have been noted by academics to facilitate referral to NGS and expand the development of related genetics services.[208] At a national level, the Health Resources and Services Administration funds the National Coordinating Center for the Regional Genetics Networks, which works with the seven accredited Regional Genetics Networks (RGNs) to develop and support a regional system to educate providers and improve patient access to genetic services, with an emphasis on access for medically underserved people.[209] RGN initiatives can increase access to genetic services based on the needs of each region, such as by developing tailored educational materials for both specialized and non-geneticist physicians and providing language interpreter training.[210,211] Thus, RGNs can leverage local infrastructure and population needs, which can ensure the development of tailored, NGS-related services and support equitable access. Overall, state governments can support the development of an environment that fosters multidisciplinary provider and collaboration of stakeholders, including industry, to increase the number and availability of genetic counselors.

POLICY RECOMMENDATION —

- **Given the limited access to specialists, the genetic testing burden falls to non-geneticist specialist clinicians. Limited knowledge of genetics and interpretation of test results continues to be a barrier to rare disease diagnosis. State-funded educational materials can guide physicians through ordering NGS and any uncertainties related to coverage of NGS.**
- **Educational materials in multiple languages could be developed by states in partnership with patient groups and providers from underserved communities to inform equitable ordering of NGS.**
- **State funding or other incentives can be used to support hospital health systems to develop multidisciplinary genetic services programs that expand physician awareness of the utility of NGS. A dedicated program can lead to an uptick in patient referrals to NGS and an increase in the number of genetic specialists employed.[212]**
- **Regional genetic service support models can efficiently increase access to NGS by facilitating relationships between states, genetics providers, non-genetic specialist providers, and patients. State governments can support the development of an environment that fosters collaboration across stakeholders, including multi-disciplinary providers and industry, to increase the number and availability of genetic counselors.**

3. Broad coverage and reimbursement can support NGS availability and access to supporting care services

To address heavy payer utilization management, several states have passed or proposed legislation mandating insurance coverage of NGS such as biomarker testing, but such legislation does not specifically encourage provision for rare disease populations.[213] California, for example, passed biomarker testing legislation (S.B. 535) that prohibits all health insurance plans from requiring prior authorization for biomarker testing for patients with advanced or metastatic stage 3 or 4 cancer or cancer progression or recurrence.[214] While this type of legislation allows states to address restrictive coverage, repeated legislative action is likely needed for coverage expansion to additional populations, such as for rare disease patients and to support access to NGS.

In addition, academic studies point to the value of laboratory support with prior authorizations and the use of patient payment assistance programs to reduce barriers related to the utilization management of NGS. One study of NGS ordering across diverse care settings found that laboratories for safety-net clinics that filed paperwork directly for Medicaid could expedite and ensure approval of reimbursement.[215] Absent this laboratory support, genetic specialists in academic medical centers experienced uncertainty about reimbursement approval and an added administrative burden. For patients with limited ability to pay for the cost of testing, payment assistance programs run by laboratories and clinical institutions can create pathways to testing despite prior authorization and reimbursement barriers. Payment support may be most beneficial to people who are enrolled in a public coverage program such as Medicare or Medicaid.[216]

While inconsistent reimbursement policies for genetic counselor services contribute to unequal access to these services, state licensure requirements also inhibit genetic counselors' ability to maximize their reach to patients.[217] Genetic counselor licensure programs can provide support and expertise to people pursuing licensure with the purpose of expanding the availability of specialists for patients. Although several states have yet to establish licensure programs, California, Florida, Pennsylvania, and Minnesota are among the 35 states with established or

pending genetic counselor licensure programs.[218] The 2022 National Society of Genetic Counselors Professional Status Survey indicates that 71% of genetic counselors are licensed to practice in one state and 54% are licensed in four or more states.[219] An interim step states could take to increase access to genetic counselor services is adopting an interstate compact to permit license reciprocity or expedite approval for genetic counselors who maintain a license in another state.[220] Without this alignment, genetic counselors face the administrative burden of registering in different states and dealing with variable state requirements for training and continuing education, which can lead to disparities and nonuniform services.[221] Cross-state licensure enables increased access by populations who may not have a sufficient number of genetic specialists in their state. The current challenges of state-specific licensure are exacerbated for telehealth providers because they can potentially engage in more interstate services than in-person providers.[222] However, genetic counselors are currently not recognized by CMS as health care providers. These challenges suggest that legislative amendments are required to support the recognition of genetic counselors as providers and enable their use of telehealth.[223]

In addition to the role of genetic counselors, other practices to meet patients' and parents' psychosocial needs relating to NGS have emerged. For example, Project Baby Manatee recommended that parents of children undergoing rWGS have access to qualified mental health professionals.[224] Both the process leading up to diagnostic confirmation and events thereafter can be psychologically distressing to parents, and children's care centers may not have the necessary staff on hand for ongoing adult support. At the state level, initiatives to understand the unmet needs of rare disease patients and caregivers in the U.S. are nascent or still underway. For example, the Minnesota RDAC recently completed a needs assessment survey of patients and caregivers, and results from the Pennsylvania RDAC's needs assessment were expected to be completed in early 2023.[225,226] While the health care community continues to learn from these assessments, legislation to ensure coverage of genetic counselors and mental health professionals could support existing patient and caregiver initiatives.

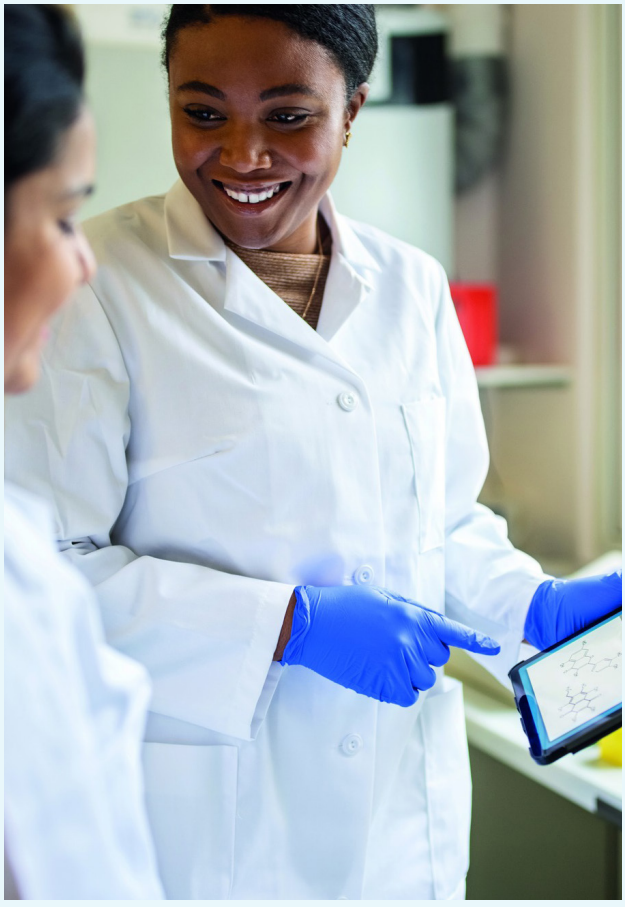
Separately, a policy approach to addressing the disincentive for hospitals to provide rWGS can be found in Michigan, where the Medicaid plan and several BCBS plans issued supplementary reimbursement or "carve-outs" for the reimbursement of rWGS. Reimbursement of the carve-out for Medicaid beneficiaries is provided directly from the U.S. Department of Health and Human Services rather than from the contracted Medicaid managed care organizations.[227,228] Similarly, a bill introduced in Minnesota (H.F. 3632, Coverage for Rapid Whole Genome Sequencing Testing) sought to establish universal coverage of rWGS for all infants with a separate payment methodology to reimburse hospitals for costs associated with rWGS; the payment would go directly from the commissioner for human services to the hospital.[229]

Several states have ensured broad coverage of rWGS for undiagnosed children in critical-care settings by leveraging recent, established cost-effectiveness data and evidence.[230] Given study findings on the spillover effects of coverage policy on payer uptake, legislation could ensure coverage of rWGS in Medicaid and state-regulated commercial insurance plans.[231,232] In addition, states could promulgate legislation to prevent excessive utilization management for tests and associated treatments, leveraging established real-world evidence to indicate the clinical scenarios in which rWGS is medically necessary for rare disease patients.

At the federal level, CMS could share best practices and evidence to support consistent evaluation of the clinical utility and cost-effectiveness of NGS of undiagnosed children and encourage state Medicaid directors to align coverage bulletins. CMS could also encourage the development of pilot programs that test the cost-effectiveness of coverage of NGS for undiagnosed adults and could provide guidance to ensure that NGS coverage decisions can evolve and be expanded as new indications require NGS. CMS could leverage findings to expand the current NCD for NGS for certain cancers to provide coverage of NGS for undiagnosed adults in certain clinical scenarios.

POLICY RECOMMENDATION —

- States could leverage recent, established data and evidence on the cost-effectiveness of rWGS for undiagnosed children in critical-care settings and pass legislation that ensures coverage of rWGS by state Medicaid programs and state-regulated commercial plans.
- States could establish legislation to prevent excessive utilization management for genetic testing, leveraging established real-world evidence to indicate the clinical scenarios in which rWGS is medically necessary for rare disease patients. States could partner with rare disease specialists and patient groups to integrate insights on health outcomes to define relevant clinical scenarios for NGS use.
- Current DRG payment rates are generally insufficient to reimburse providers and hospitals for the cost of NGS and interpretation. State legislation could establish supplemental payments or health plan carve-outs to further reimburse hospitals for the provision of rWGS. Establishing supplemental payments or carve-outs can support broad provision of rWGS that is aligned with cost-effective, evidence-based practices.
- States without licensing programs could establish licensure or interstate compacts that support the licensure of genetic counselors to overcome the lack of federal recognition, specifically by CMS, of genetic counselors as health care providers with coverage.
- CMS could encourage state Medicaid programs to cover genetic counseling services in multidisciplinary teams to support people with rare disease and their caregivers in accessing relevant information and otherwise navigating the health care system. CMS's recognition of genetic counselors as health care providers could also enable access to and coverage of counseling services via telehealth through existing telehealth coverage laws.
- CMS could share evidence and best practice guidance with state Medicaid directors to support consistent evaluation of the clinical utility and cost-effectiveness of NGS for undiagnosed children. CMS could encourage Medicaid programs to align coverage bulletins.
- CMS could encourage the development of pilot programs to evaluate the cost-effectiveness of covering NGS for undiagnosed adults. CMS could leverage findings to expand the current NCD beyond certain cancers to provide coverage of NGS to undiagnosed adults in certain clinical scenarios. There is evidence that the Medicare NGS NCD for certain cancers has a spillover effect on commercial plan coverage policies.[233]



4. Expand health system capacity for genomic data storage and protection to address patient data privacy concerns and support NGS uptake

Policy initiatives that address privacy concerns consist of legislation to protect against sharing and misuse of patient data. However, there is a need for broader implementation of patient-centric measures that aim to support informed consent and shared decision-making and enable patients to know how data will be accessed, used, and returned.[234] Examples of patient-centric initiatives to allay data-sharing concerns include the following:

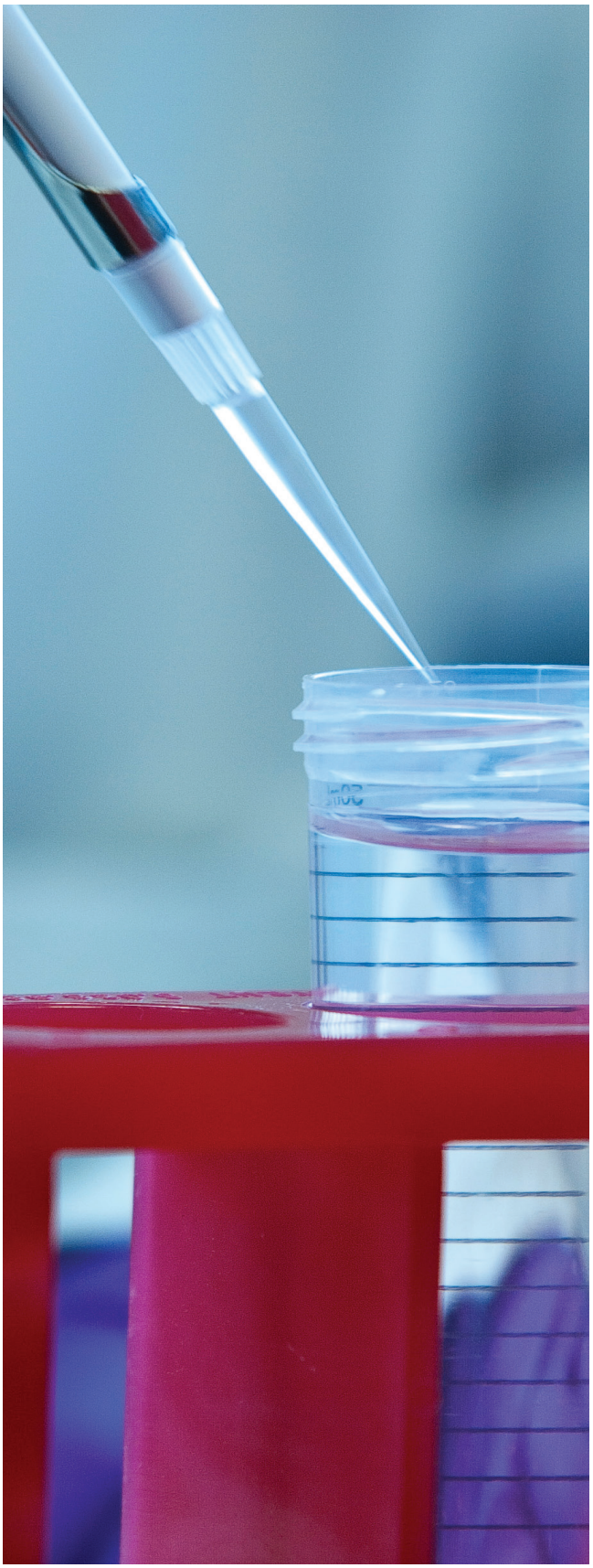
- **The National Institutes of Health (NIH) Genomic Data Sharing Policy** sets guidelines on how to protect research participant privacy while still allowing the scientific community to access and share data.[235] Further, the NIH issues certificates of confidentiality to assure research participants of their privacy.
- **The Mayo Clinic** in Minnesota uses informed consent and established data use guidelines to integrate the data with its EHRs for clinical use and for ongoing research.[236]
- **The Geisinger** Health System's MyCode screening program has tested, through PCPs and genetic counselors, a patient notification model that respects patients' privacy and mitigates undue psychological distress about gene mutations that are not clinically meaningful.[237] To maintain patients' agency regarding information sharing, the Geisinger model also provides materials to them that they can use to communicate information about rare disease risk with family members.
- **Rare-X**, a nonprofit patient advocacy health tech organization, uses a patient-owned online data collection portal as part of its platform for genomic data gathering, structuring, sharing, and analysis for both clinical and research use.[238] This online portal gives patients easy access to their data and decision-making opportunities.
- **The Rare Diseases Cure Accelerator – Data and Analytics Platform (RDCA-DAP)**, launched by the Critical Path Institute in partnership with NORD and with Food and Drug Administration (FDA) grant funding, is an independent data collaboration and analytics hub that curates and aggregates rare disease data for research while respecting original data rights and the ownership policies of contributing organizations.[239]
- **Academics** have advocated for the expansion of the GINA and other existing regulations to protect against broad health insurance and employer discrimination.[240] Some states, such as California, have passed additional laws expanding the scope of GINA to support broader uptake of NGS.[241]

In addition, potential policy solutions to address data infrastructure challenges and expand the clinical use of NGS for disease diagnosis can be seen in California, where the Precision Medicine Advisory Committee is pioneering a public-private collaboration to advise policy makers on a holistic plan for the widespread adoption of precision medicine. The strategy includes a multiyear plan to develop infrastructure for digital storage and linkage to EHRs across the state.[242] In addition, health systems, including the Mayo Clinic and HealthPartners in Minnesota and Geisinger in Pennsylvania, have begun to integrate genomic data with their EHRs to support clinical decision-making.[243,244,245] Furthermore, federal initiatives that aim to support rare disease genomic patient data collection and diagnosis include the GREGoR Consortium, which is funded by the National Human Genome Research Institute (NHGRI) within the NIH. The Consortium aims to facilitate data sharing, collaboration, and an increased focus on the application of new sequencing strategies and analytical approaches to support disease diagnosis.[246] However, we find no evidence of a cohesive national registry for providers to query when diagnosing a patient.

POLICY RECOMMENDATION —

- States could leverage existing genomic data protection legislation, such as the GINA, and address gaps to support broader uptake of NGS.
- States could fund the upgrade of health systems' genomic data storage capacity and make it a priority by establishing precision medicine access goals, developing a long-term plan, and ring-fencing investment for initiatives that expand the use of NGS for rare disease diagnosis.
- CMS and NIH could develop NGS-usage guidelines that support informed consent and patient control over data for Medicare and Medicaid beneficiaries (e.g., express consent for data usage, systems that enable patient control over data, and pathways to rescind consent).

The policy recommendations presented in this report reflect opportunities to shorten the rare disease diagnosis odyssey. These recommendations are broad and far-reaching, and any implementation will require further assessment of the benefits and unintended trade-offs.



KEY TERMS/GLOSSARY

Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease.[247]
Centers for Medicare and Medicaid Services (CMS)	A federal agency within the United States Department of Health and Human Services that administers the Medicare Program and oversees the federal portion of the Medicaid Program, the State Children's Health Insurance Program (SCHIP), and other health-related programs.[248]
Chromosome	A structure inside the nucleus of a cell consisting of proteins and DNA organized into genes; each cell normally contains 23 pairs of chromosomes.[249]
Covered benefits	A health service that is included (i.e., "covered") under the premium for a given health insurance policy that is paid by, or on behalf of, the enrolled patient.[250]
Diagnosis-Related Group (DRG)	A patient classification scheme that provides a means of relating the case mix of patients a hospital treats to the costs incurred by the hospital; in the DRG system, insurers pay the provider hospital for a procedure or diagnosis.[251]
Diagnostic odyssey	The protracted journey toward diagnosis for people living with rare diseases.[252]
Electronic Health Record (EHR)	An electronic version of a patient's medical history that is maintained by the provider over time and may include all the key administrative clinical data relevant to that person's care under a particular provider.[253]
Exome	The sequence of all the exons in a genome, reflecting the protein-coding portion of a genome; in humans, the exome is about 1.5% of the genome.[254]
Exon	A region of the genome that ends up within an mRNA molecule; some exons are coding—they contain information for making a protein—whereas others are non-coding.[255]
Gene-sequencing panels	Tests that detect known and novel variants in selected sets of genes or genomic regions.[256]
Genetic counselor	Medical professional with advanced training in medical genetics and counseling to guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families and how to interpret genetic test results based on family history.[257]
Genome	The entire set of DNA instructions found in a cell, consisting of 23 pairs of chromosomes located in the cell's nucleus in humans and a small chromosome in the cell's mitochondria.[258]
Medicaid Program	A state-administered program that pays for health insurance for low-income individuals.[259]

KEY TERMS/GLOSSARY

Medical geneticist	A doctor who specializes in diagnosing and treating genetic disorders or conditions and who can counsel individuals and families at risk for certain genetic disorders or cancers.[260]
Medicare Program	A federal program that pays for health insurance for people 65 or older and for some younger people with disabilities.[261]
National Coverage Determination (NCD)	A national policy issued by the CMS that determines whether Medicare will pay for a medical service or item.[262]
Newborn screening (NBS)	Screening programs that identify conditions that can affect a child's long-term health or survival.[263]
Next generation sequencing (NGS)	Refers to large-scale DNA sequencing technology that allows for querying the entire genome, the exons within all known genes, or only exons of selected genes.[264]
Rapid whole genome sequencing (rWGS)	Refers to the sequencing of nearly the entire genome simultaneously, coupled with a focused phenotype-driven analysis of WGS data, to make a provisional molecular diagnosis in one day.[265]
Rare disease	A disease or condition that affects fewer than 200,000 people in the United States, as defined by the Orphan Drug Act.[266]
Rare Disease Advisory Council (RDAC)	An advisory body that gives the rare disease community a stronger voice in state government by giving various stakeholders the opportunity to make recommendations to state leaders.[267]
Reimbursement	The payment received by a health care provider, hospital, diagnostic facility, or other health care facility for providing a medical service.[268]
Whole exome sequencing (WES)	Refers to the sequencing of 95% of the exome, the coding region of the genome.[269]
Whole genome sequencing (WGS)	Refers to the sequencing of nearly the entire human genome simultaneously.[270]

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