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The Influence of Social Determinants of Health on the Genetic Diagnostic Odyssey: Who Remains Undiagnosed, Why, and to What Effect?

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Abstract

Although Mendelian genetic disorders are individually rare, they are collectively more common and contribute disproportionately to pediatric morbidity and mortality. Remarkable advances in the last decade have led to identification of the precise genetic variants responsible for many of these conditions. Confirming the molecular diagnosis through genetic testing allows for individualized treatment plans in addition to ending the diagnostic odyssey, which not only halts further unnecessary testing but also may result in immense psychological benefit, leading to improved quality of life. However, ensuring equitable application of these advances in genomic technology has been challenging. Though prior studies have revealed disparities in testing for genetic predisposition to cancer in adults, little is known about the prevalence and nature of disparities in diagnostic testing in the pediatric rare disease population. While it seems logical those with impaired access to healthcare would be less likely to receive the genetic testing needed to end their odyssey, few studies have addressed this question directly and the potential impact on health outcomes. This review synthesizes the available evidence regarding disparities in pediatric genetic diagnosis, defining the need for further, prospective studies with the ultimate goal of delivering precision medicine to all who stand to benefit.

Introduction

Although Mendelian genetic disorders are individually uncommon, such rare diseases are collectively common and estimated to affect a substantial proportion of the global population, with a cumulative prevalence of at least 1.5–6.2% (1). The morbidity and mortality burden of these rare conditions is disproportionate to their prevalence, with

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congenital anomalies and genetic conditions representing the leading cause of infant mortality in the United States (2) and causing substantial global impact as well (1, 3). Many rare disorders have an underlying genetic basis, with Mendelian disorders, or conditions due to a change at a particular single genetic locus, accounting for a large proportion of these (1). Others may have an underlying genetic basis that is non-Mendelian, or attributable to changes at multiple loci or following atypical inheritance patterns. This distinction is important to consider, as much of our clinical and research diagnostic genetic testing ability currently focuses on Mendelian conditions, particularly those that are monogenic, or attributable to pathogenic variation in a single gene. Indeed, with the rise of massively-parallel (“next generation”) sequencing in the last decade, over one thousand of novel disease genes have been recognized, leading to the ability to find a molecular diagnosis for many individuals (4). Particularly, exome sequencing (ES), in which the coding regions of the genome are sequenced and analyzed for disease-causing changes in a “hypothesis-free” approach, has revolutionized clinical genetics by finding diagnoses in weeks to months that historically may have taken years to identify, if at all. It is important to note, however, that even with these remarkable advances, more than half of patients suspected to have a rare genetic disorder remain undiagnosed (5).

The benefits of a molecular genetic diagnosis, identifying the precise underlying genetic change responsible for a rare disease, are numerous. While the diagnosis may have been suspected clinically, the molecular confirmation allows providers to proceed confidently with a management plan tailored to the individual. Certain medications may be indicated or contraindicated (including those that are commonly used and low cost) (6), and organ or stem cell transplants may be available for certain conditions in addition to emerging therapies that are gene or variant-specific (7). For conditions with a poor prognosis, confirming the diagnosis may help caregivers appropriately counsel families on their goals of care (8). Furthermore, accurate identification of a molecular genetic diagnosis prior to birth may assist in pregnancy management decisions and can also contribute to future reproductive decision-making (9). Finally, there are both economic and psychological benefits to ending the diagnostic odyssey which, though they are difficult to quantify, are at least equal in importance to any other benefit previously mentioned (10, 11).

As with other technological advances, however, the benefits of this revolution within clinical genetics have not been universally realized. Though equally affected by Mendelian genetic disorders, underrepresented minorities in the U.S. appear to be less likely to receive a molecular genetic diagnosis (12). Clinical genetic testing both for predictive and diagnostic purposes is underutilized in minority populations due to issues with access and may be nondiagnostic due to challenges in results interpretation (12-14). To the first point, underrepresented minorities have diminished access to care compared to their White peers, and thus are less often seen by clinical genetics providers (15) and subsequently less likely to have diagnostic testing sent. To the second, even if testing is performed, the results may be difficult to interpret due to the lack of understanding of normal genetic variation in racial and ethnic minority populations (12). A striking example of the consequences of such disparities is diagnosis of cystic fibrosis for non-White children, a diagnosis requiring prompt recognition and treatment, where diagnoses have been delayed in minority individuals due to lack of suspicion of this condition, lack of appropriate newborn screening,

and deficiencies in test interpretation (16-20). We therefore reviewed the existing literature regarding disparities in genetic diagnosis and examine the reasons for these disparities in the context of this interpretative framework.

Race versus Ancestry

It is paramount in a discussion of racial and ethnic disparities in healthcare, especially in the field of genetics, to clearly state that race is a social, and not biologic or genetic category (21). The concept of race emerged in the sixteenth and seventeenth centuries to explain differences seen between European explorers and “uncivilized” and “immoral” people encountered in the New World. These categorizations, defined by physical characteristics, were inherently designed to establish hierarchies of power imbued with value (21, 22). In the modern era, an investigation of the racial classifications in the United States census reveals that race is neither permanent over time nor devoid of sociopolitical motivation (23). Ultimately, race is a social construct that categorizes people by stereotyped physical characteristics to establish hierarchies of power predicated on the value of exclusionary practices in which the dominant group (White race) subverts all others (22). The discussion of race and, relatedly, ethnicity, becomes increasingly difficult in the field of clinical genetics where a torrid history of medical experimentation and eugenics greatly impacts our ability to discuss important issues related to race, in particular inequities in care.

Importantly, genetic ancestry is defined separately from race and refers to a genetic background that is shared among individuals because they have descended from common ancestors. Ancestry can be imputed from genomic sequencing studies in a way that race cannot be because race is socially, and not genetically, defined. For example, direct-to-consumer genotyping assays can inform an individual that they are of Eastern European, Mediterranean, and African descent but not that they are Black. Although individuals identifying within the same racial or ethnic group may also share common ancestors, neither race nor ancestry should be taken as a surrogate marker for the other. This confluence of race, ancestry, and genomics has been recently well-described elsewhere (24). However, while race is a social construct, the lived experience and impact of race on health and health services utilization is real and measurable. In this review, we focus particularly on disparities in genetic testing among underrepresented minorities with regard to race and ethnicity.

Disparities in Genetic Diagnosis in Practice

Underrepresented minorities are less likely to have a genetic diagnosis identified

Precision medicine is multi-faceted and can occur in a variety of contexts. For the purposes of this review, we discuss precision medicine as it applies to rare genetic disorders rather than to the genetics of common diseases – where genotyping (determining the pattern of common variants in an individual) and polygenic risk scores are used to assess the risk of relatively common conditions that are multifactorial in etiology, such as cardiovascular disease or preterm birth. For pediatric patients with rare diseases, a precision medicine approach involves using diagnostic genetic testing to identify a pathogenic variant (often in a single gene or chromosome) and using this diagnosis to guide management. Identifying a diagnosis of a Mendelian disorder is typically achieved using testing such as chromosomal

microarray analysis, which can identify gains or losses of chromosomal material encompassing pieces of genes or several genes, or massively-parallel sequencing, used to identify single nucleotide variants or small insertions/deletions in single genes, often through gene panel testing or exome sequencing. Treatments can be tailored not only to a particular gene, but even to a particular variant, as has been shown in the recent use of antisense oligonucleotide therapy to treat a young girl with Batten's disease, a neurodegenerative condition (7). However, even if such a treatment is not available, identifying the underlying genetic change responsible for disease allows for clarity in management and medical decision-making.

Few studies have assessed the influence of social determinants of health on the ability to identify a Mendelian genetic disorder in the pediatric population. While certain populations are geographically or socially insular and have higher rates of recessive conditions due to a founder affect, such as the high prevalence of conditions such as Tay Sachs disease in the Ashkenazi Jewish community, or a high rate of recessive disorders found in sequencing highly consanguineous populations (25), many other recessive genetic conditions are not more frequent in any particular community, and many genetic disorders result from de novo variants, or those that arise spontaneously in the affected child. In general, rare genetic disorders should affect various racial, ethnic, and socioeconomic groups indiscriminately. Furthermore, because race is a temporally evolving social construct that has no genetic basis, there should not be a lower prevalence of genetic conditions within the underrepresented minority community. And yet, genetic diagnoses are less likely to be identified in racial and ethnic minority individuals. A study of thousands of people undergoing genetic testing for cardiomyopathy found that underrepresented minorities were less likely to have a diagnostic result and more likely to have an inconclusive result (12). Genetic leukodystrophies, neurodegenerative conditions caused by rare loss-of-function or missense variants in single genes – that in many cases are treatable if found early – were identified less often in non-White than in White individuals in a large pediatric hospital database, despite no difference in the rates of loss-of-function or missense variants in these populations (13). A recent study examining the use of exome sequencing versus standard clinical testing in infants found that Hispanic infants, though comprising nearly half of the cohort, were less likely to have a diagnosis found by either etiology (26).

Also intriguing is that many recent, large-scale reports of the yield of clinical exome sequencing (8, 27, 28) for pediatric patients in the United States do not present data on the racial breakdown of their study populations, thus it is impossible to identify possible disparities in access to this technology. One study describing the overall yield of the clinical genetic evaluation in an outpatient setting reported approximately one third underrepresented minorities but does not comment on whether underrepresented minorities were more or less likely to find a diagnosis (5). It is possible that race is not often reported in large cohort studies describing ES results because it is not thought that race should influence the diagnostic approach or yield (and appropriately so). However, this information would be helpful in identifying discrepancies in access to care: it would be important to know if underrepresented racial minorities are well-represented in the studies reporting high diagnostic yields using ES. For, while the sequencing and analysis of ES data is race blind, access to ES is not. Indeed, a call for increased consideration of race and ethnicity in

medical genetic literature was published several years ago, noting that even journals with a high impact factor frequently did not adhere to ideal practices related to the use of race and ethnicity in research (29). As the available literature suggests that underrepresented minority populations are less likely to have a molecular genetic diagnosis made, we now discuss the reasons for this apparent discrepancy.

Barriers to Access of Clinical Genetics Services

A genetic diagnosis may not be suspected in underrepresented minority individuals

Multiple steps are required for a genetic diagnosis to be suspected and ultimately confirmed (the “diagnostic odyssey”), and underserved populations are likely to be missed at each step along the way (Figure), which results in fewer diagnoses identified. Although disparities in genetic testing have been well defined in adult populations at risk for hereditary cancer syndromes (30), for the pediatric rare disease population, an additional challenge exists. Whereas adult patients at risk for hereditary cancer predisposition syndromes present with a high-risk malignancy prompting genetic testing, the presentation of a pediatric patient with a genetic syndrome may be more subtle. Many children have developmental delay or intellectual disability, or other relatively nonspecific neurologic complaints such as seizures or hypotonia. Other children may present with congenital anomalies which may or may not be genetic. Distinguishing between idiopathic developmental delay or isolated congenital anomalies and those occurring in the setting of an underlying genetic syndrome can be challenging. Suspecting a genetic diagnosis may be contingent upon pathognomonic facial features which have been defined and catalogued in White European individuals. Thus, underrepresented racial and ethnic minority patients may not exhibit the “classic” facial features described for certain disorders (31, 32) and may be less likely to be referred to a clinical geneticist. This may be particularly likely to occur for children with complex healthcare needs who have other underlying conditions that could explain features such as seizures, developmental delay, or weakness (such as infection, birth injury or history of preterm birth) (33). Ideally, this bias against recognition of a genetic disorder in certain populations will improve as medical texts and dysmorphology atlases are developed to include diverse populations (34, 35) and through other initiatives such as the Pilbara Faces project (a resource developed in Australia to identify dysmorphology syndromes in indigenous populations) and journal calls for publications on presentations in diverse populations (36). Additionally, children from underserved communities may have their developmental concerns attributed to adverse childhood events (ACES), which, though a valid concern, may bias providers against suspecting an underlying genetic syndrome. Of course, these two contributors are not mutually-exclusive and the co-occurrence of ACES and a genetic disorder could result in a particularly detrimental outcome if neither is identified. Childhood adversity has also been found to result in a later age at autism diagnosis related to issues with healthcare access which is the case for genetic syndromes as well (37).

Underrepresented minority children have impaired access to clinical genetics services from the clinic to the testing laboratory

Another reason that children who belong to underrepresented minority groups are less likely to receive a genetic diagnosis is impaired access to clinical genetics services. Once suspicion for an underlying genetic disorder has been raised, a referral is usually made for a clinical genetic evaluation by a pediatric geneticist (Figure). Overall, clinical genetics providers are scarce and concentrated in certain areas of the country, typically close to large academic centers (38, 39). However, even if clinical genetic services do exist in a certain region, referrals for testing may be made less often for underserved populations. This has been demonstrated in the adult internal medicine community, where underrepresented minority patients are less likely to be aware of (40) and tested for hereditary cancer syndromes (e.g. *BRCA1* or *BRCA2* testing for breast and ovarian cancer risk) (30). The reasons for this discrepancy may be related to level of education, knowledge of genetic testing, trust in providers, or insurance coverage as has been shown in one study (41), though, interestingly, racial discrepancies have been shown to persist independent of socioeconomic status or insurance which reflects potential provider bias in referral (30, 42). It is also possible that among the multiple challenges faced by the parents of children with complex medical needs who may have underlying genetic disorders, identifying the molecular diagnosis is not a priority. Providers may instead focus on management of symptoms, which on their own may require multiple specialty visits that are difficult to manage. Additionally, pediatric providers, understanding the impact of ACES and the importance of social determinants of health on promoting healthy development, may focus on addressing food or housing insecurity if present rather than pursue a pediatric genetics consultation. This viewpoint is problematic as it suggests a particularly patronizing form of bias and fails to recognize the ways in which a genetic diagnosis can improve quality of life for a family, via improved access to services and other supports, for example (43).

Even if a referral to genetics is made, families living in underserved areas or identifying as underrepresented minorities may not complete this referral. A recent study demonstrated that only half of subspecialty referrals from a large academic center were successfully completed within 90 days. Those with public insurance, lower median income, or of African American race were less likely to schedule and complete the appointment (15). Importantly, this study categorized outpatient genetics services as “low-capacity” (fewer providers and appointments available), and when compared to other subspecialties, genetics clinics had a high proportion of referrals that were never even scheduled, though the small proportion of visits that were scheduled were generally attended by the family (15). Possible reasons that a referral would be made but not scheduled are lack of desire on the part of the family to make an appointment (perhaps related to a lack of understanding as to why the appointment is necessary or concerns regarding cost), or a lack of available appointments that are compatible with the family’s schedule (particularly a problem for “low-capacity” subspecialties). Such challenges are not unique to the United States, as substantial barriers to access of clinical genetics services resulting in delays in diagnosis are present throughout the world (31, 33, 44).

Finally, even when a family presents to a genetics clinic and testing is recommended, there are multiple barriers that persist. Often, multiple visits are required before a blood sample is drawn for genetic testing, due to the need to pursue insurance authorization or the need to schedule a separate visit to consent for a test such as exome sequencing. Furthermore, the parents, in addition to the child, may need to be tested to fully interpret test results, presenting another barrier to successful genetic diagnosis as it is often difficult for family members to make multiple trips to the laboratory. Other follow-up evaluations such as laboratory or radiologic studies may also be needed to evaluate a genetic testing result and these, too, are more difficult for families in underserved areas to complete. The ability to be fully evaluated by a geneticist and ultimately find a molecular diagnosis thus may require a substantial amount of time and effort, both of which may be limited among those with less access to care. Also important are fear, mistrust, and cultural beliefs which may lead to reluctance for genomic analysis of blood samples – for example, not wanting to undergo any testing that removes tissue from the body (45).

Barriers to Interpreting Genetic Testing Results

Underrepresented minorities may be more likely to have nondiagnostic genetic testing results

Even when access to clinical genetics services are enabled and all recommended diagnostic tests sent, many individuals belonging to underrepresented minority groups may still have inconclusive results, due to the decreased ability to interpret the pathogenicity of variants in certain populations categorized by ancestry. This contributes to disparities in diagnostic rates. It is important to view these categories in terms of ancestry, as race categorizes individuals from shared and disparate historical and geographical migration. For example, when considering the Black population in the United States, this racial category embodies populations that migrated to the U.S., in the setting of involuntary oppression and slavery as in the case of African Americans from West Africa, as well as in the setting of migration fueled by natural disasters and sociopolitical compromise, as in the case of the U.S. Haitian immigrant population. While race is not synonymous with ancestry as previously discussed, race continues to be a population defining and categorizing construct and certain subpopulations within racial categories may share common ancestors. Indeed, the concepts of race and ancestry are often conflated in research on genetic testing, as is seen in multiple publications describing lower rates of pathogenic *CFTR* variant detection (conferring a diagnosis of cystic fibrosis) in non-White (Black, Hispanic, Asian) compared to White populations; the populations in these analyses are characterized by self-reported race and demonstrate higher frequencies of non-“deltaF508” pathogenic variants in non-White racial groups (16, 18).

Regardless, understanding the frequency of a particular genetic variant within a population is paramount to appropriate diagnosis. Because defining the frequency of a variant in a healthy population is essential in order to interpret its pathogenicity (variants that occur commonly should not cause a rare, severe, pediatric-onset disease), the availability of population-based genomic data is important in order to make accurate molecular genetic diagnosis. Variants are often re-classified in minority populations (defined by ancestry) as understanding of

common variants within these sub-populations increases and variants once thought to be disease-causing are found to occur with great frequency in healthy individuals (46, 47). Conversely, it is difficult to establish that a variant is **not** benign unless similar variants have been reported in affected individuals, and diversified population data is essential for this purpose as well (47). Thus, as previously mentioned, underrepresented minorities on the basis of ancestry have been found to more often have non-diagnostic test results (12), at least some of whom may actually harbor a disease-causing variant. Increasing the diversity in population databases and genomic biobanks on the basis of ancestry would be instrumental in improving the interpretation of genetic testing results. Although race and ancestry are overlapping concepts as demonstrated by the cystic fibrosis studies (16, 18), they have important distinct attributes and are not interchangeable, as we have previously discussed. However, due to the overlapping nature, it is likely that diversifying the racial pool in population studies will also diversify the ancestry pool.

The Role of Research

Current research reports insufficient numbers of underrepresented minority participants

If the clinical genetic diagnostic odyssey is unrevealing, many will turn next to research, where multiple rare disease genomic sequencing initiatives have resulted in high solve rates for undiagnosed individuals through the identification of previously undiscovered variants or novel disease genes (4, 48, 49). However, genomic sequencing research studies for predictive (50, 51) or diagnostic (48) purposes report low rates of minority participants. The Undiagnosed Diseases Network (UDN), to which rare disease patients are referred by their providers, reports no difference in rate of acceptance on the basis of race, but referred patients are overwhelmingly (>80%) White and Non-Hispanic (52). As most UDN referrals are from primary care providers (52), this under-representation of minority groups in UDN referrals likely mirrors the lack of referrals to genetics clinics. Thus, just as they are not being diagnosed through the clinic, minority populations are also not finding answers through sequencing as part of research studies (48). For studies that do not require provider referral, such as the MedSeq study in which participants are randomized to receive genomic sequencing or usual care, low participation of underrepresented minorities is also seen (53). This reflects, among other things, a general underrepresentation of minority populations in clinical research for reasons that have been well-discussed elsewhere and are outside the scope of this review (54, 55). Clearly, more work is needed to involve diverse populations in the research studies that are going to inform and drive clinical practice patterns.

Downstream Effects and Future Directions

Many studies have documented the effect of a molecular genetic diagnosis on clinical care (8, 9, 48, 56, 57). However, the reality remains that for many conditions, management is supportive, aimed at supporting development and screening for possible health complications, with no precise therapy or “cure” available. While some may question the benefit of identifying a molecular diagnosis for children with complex medical needs if this diagnosis will be explanatory but not prevent or reverse disease manifestations, other benefits of a molecular diagnosis may include accurate reproductive counseling to promote

the health of future children in addition to informed medical decision-making, including goals of care and decisions regarding the provision or withdrawal of life-sustaining technology for critically ill children. Furthermore, gaining understanding and insight into a child's condition may provide immeasurable psychosocial benefit (58, 59), or "personal utility", in addition to "informational utility" – being able to access support groups and relevant educational resources (60). Conversely, remaining genetically undiagnosed confers substantial psychological burden to patients and their families (10, 11, 61). However, just as studies concerning the diagnostic yield and clinical utility of genetic testing report low numbers of underrepresented minority participants, the studies establishing this psychological burden of remaining undiagnosed disproportionately include non-Hispanic White participants that tend to be of higher socioeconomic status (10, 11, 61). Parents whose children remain undiagnosed have reported high rates of anxiety and depression, though this cohort was 86% Caucasian (10), while another study reported feelings of uncertainty surrounding the diagnosis leading to poor coping and adaptation in a cohort that is 91% White and 96% non-Hispanic (61). Parents whose children received a molecular genetic diagnosis revealed that they felt that the results impacted care and allowed them to connect with support groups and research in addition to reporting psychological benefit, though these parents were predominantly non-Hispanic White (67%), with most holding jobs (64%) and advanced educational degrees (71%) (62). It seems clear that many parents whose children remain genetically undiagnosed experience a certain degree of distress related to uncertainty that may be ameliorated by finding a molecular diagnosis, though to what extent this is generalizable to all families is unclear. Some may posit that if a parent's main concern is access to basic healthcare, as may be the case in underrepresented minorities, or housing or food insecurity as in the case of families from lower socioeconomic position, the lack of a genetic diagnosis may not be as heavy a burden. However, such arguments excuse inequities in care, assert judgment, and claim racial differences in basic value systems. Such arguments attempt to justify and excuse, and subsequently propagate inequity and disparities in care. Alternatively, we believe that all children regardless of race or socioeconomic standing should have equal access and diagnostic yield from genetic testing and that further research on diagnostic impact should make extra effort to be inclusive of diverse populations.

Certainly, the diagnostic odyssey can be lengthy and costly for many rare disease patients, though for many underrepresented minority individuals, this odyssey is either more arduous or never even initiated. Although the derailment in the diagnostic odyssey may be linked to one misstep, as illustrated in the Figure, for many individuals, breakdowns may occur at many points along the way (as in the example of cystic fibrosis). To truly inform further advances in genomic medicine, these disparities in genetic diagnosis must be further understood, as well as their impact on the lives of all children and their families.

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Impact:

- Social determinants of health are known to contribute to inequality in outcomes, though the impact on pediatric rare disease patients is not fully understood
- Diagnostic genetic testing is a powerful tool, though may not be available to all in need
- This article represents the first effort, to our knowledge, to evaluate the existing literature regarding disparities in genetic testing for pediatric rare disease diagnosis and identify gaps in care

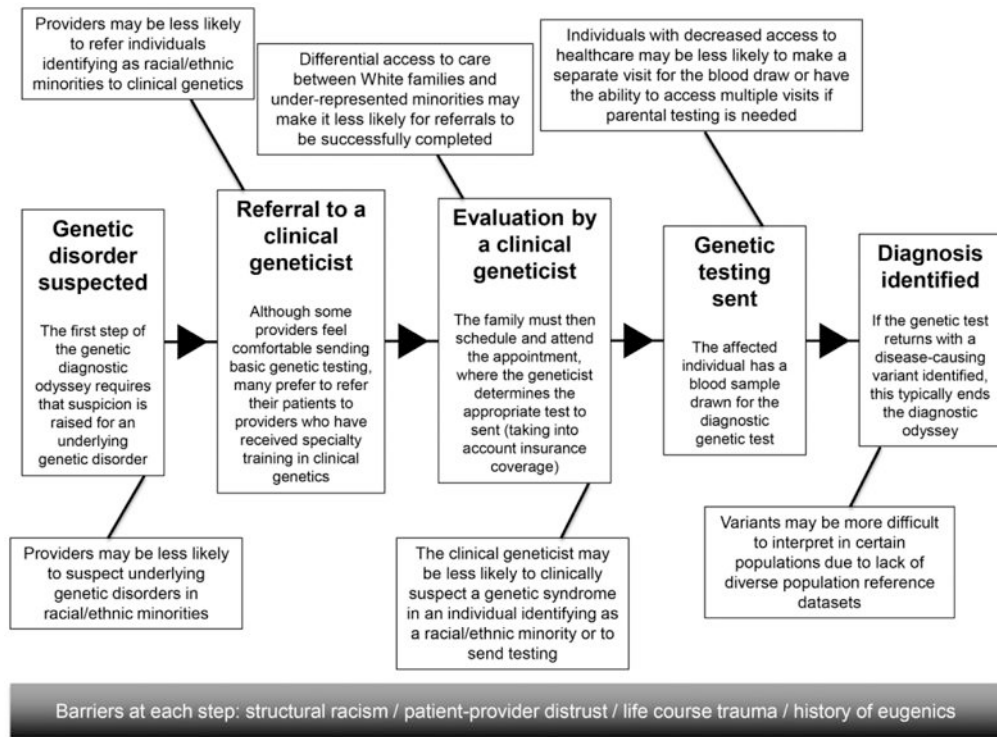


Figure. Illustrating the process of identifying a genetic diagnosis for rare disease patients and the possible interference of social determinants of health.