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Precision Medicine and Health Disparities: The Case of Pediatric Acute Lymphoblastic Leukemia

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Abstract

Precision medicine seeks to improve health care by individualizing treatment based on a person's genetic predispositions, lifestyle, and environment. While this approach holds great promise for improving health care, its potential relevance to population health disparities is not clear. Pediatric acute lymphoblastic leukemia provides an example to illustrate the complexity of the issue. African American (AA) children have a lower incidence of acute lymphoblastic leukemia (ALL), due in part to a lower prevalence of gene variants associated with risk, but experience higher relapse rates than European American (EA) children after treatment. AA children are also more likely to present with poor prognostic indicators at the time of diagnosis. Numerous environmental exposures have been associated with ALL risk, but effect sizes are small and studies are lacking to assess whether differential exposure could account for the observed racial disparities. Gene variants associated with treatment response can partially account for higher relapse rates in AA children. This finding could reflect the optimization of current chemotherapy regimens in predominantly EA populations. Importantly, the higher relapse rate seen for AA children in national data was not observed in a care setting that included elimination of out of pocket costs, risk-directed therapy based on stringent risk stratification, and rigorous case management. The ALL example illustrates the importance of social factors in addressing health disparities, including access to effective treatment and inclusion of diverse populations in research, but also points to important ways in which precision health research can help to illuminate disease processes and contribute to improving effective treatment for all patients.

Introduction

Precision medicine seeks to improve health care by individualizing treatment based on a person's genetic predispositions, lifestyle and environment (Precision Medicine Working Group). The central premise is that genetic and other biomarkers can be used to improve diagnosis and risk assessment, leading to personalized treatment and prevention (Precision

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Medicine Working Group; Feero et al., 2018; Ashley, 2016), and ultimately to broad improvement in opportunities for health (Collins and Varmus, 2015). A host of new genetic tests, notably tests to predict cancer risk and inform drug therapy, demonstrate the potential benefit of this paradigm (Ginsburg and Phillips, 2018). But can it address the problem of health disparities?

Healthy People 2020 defines a health disparity as “a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.” (Healthy People 2020). This definition would seem to provide little room for a contribution from precision medicine. Rather, investments in social determinants of health such as access to education, employment, basic health care, safe housing, and a clean environment provide a more direct and productive approach to population health (Braun, 2002; Joyner and Paneth, 2019; Bravemen and Gottlieb, 2014). However, Khoury and Galea point out that improvements in individual health care can be complementary to population-based efforts; that risk stratification within populations might improve prevention efforts; and that precision approaches need not be limited to drug or gene-focused approaches (Khoury and Galea, 2016). Others have argued that it would be unwise to ignore the potential contributions of genomics, noting that population genetic variation may result in differences in disease susceptibility that influence disparities (Burchard et al., 2003; Ramos and Rotimi, 2009), and that genetic analysis offers a powerful tool for evaluating disease biology and clarifying “the complex interplay that creates health disparities” (Bustamante et al., 2011). We use the example of racial disparities in outcomes for childhood acute lymphoblastic leukemia (ALL) to explore these complexities, with the goal of identifying how precision health research might contribute in addressing this and other health disparities.

We focus on a cancer example because cancer is an important target for precision medicine. Genetics plays a key role in cancer biology (Weinstein et al., 2013; Pui et al., 2018). The malignant process reflects the accumulation of genetic changes within a clone of cells, leading to uncontrolled growth and metastatic spread. Importantly, these genetic changes result from a mix of causal factors. Inherited susceptibility can lead to both modest and substantial increases in cancer risk (Ginsburg and Phillips, 2018). Additionally, cancer initiating or promoting somatic mutations may occur, sometimes as a result of exposure to mutagens such as radiation or other environmental toxins (Schuz and Erdmann, 2016). Lifestyle factors such as cigarette smoking (which delivers mutagenic compounds) and alcohol use can also contribute, depending on the cancer. Finally, environmentally induced epigenetic changes, such as DNA methylation, can lead to carcinogenic changes in gene expression (Timms et al., 2016).

Acute lymphocytic leukemia (ALL) disparities

ALL has an incidence of approximately 30 cases per million person-years (Lim et al., 2014), or a roughly 1 in 2000 likelihood of occurring between 0 and 15 years (Inaba et al., 2013). National surveillance data document persistently higher relapse rates for African American (AA), as well as for Native American and Hispanic children, compared to Asian and European American (EA) children (Kadon-Lottick et al., 2003; Pui et al., 2012), despite refinements in treatment that have led to a US survival rate exceeding 90% (Pui et al., 2018). Two other characteristics differentiate ALL in AA children. First, counterintuitively, African American (AA) children have a lower incidence of ALL, approximately half that of European American (EA) children (Lim et al., 2014). However, AA children are more likely to have poor prognostic indicators at the time of diagnosis of ALL, including a higher rate of high leukocyte counts, unfavorable T-cell immunophenotypes, the chromosomal translocation t(1:19) with E2A-PBX1 fusion, and a lower rate of hyperdiploid blast cells (Pui et al., 2003).

Do ALL relapse rates fit the Healthy People 2020 definition of a health disparity?

The reasons for the higher ALL relapse rate among AA children are not fully understood, but one observation suggests that this health difference is, in the Healthy People 2020 definition, “closely linked with social, economic, and/or environmental disadvantage” (Healthy People 2020). The higher relapse rate seen nationally for AA children has not been observed at a leading pediatric cancer center. St Jude Children’s Research Hospital in Memphis TN reports no difference in relapse rate for AA and EA children, despite the generally poorer prognostic profile among AA children at the time of diagnosis (Pui et al., 2003; Pui et al., 2012). Two aspects of care at St. Jude Hospital offer a potential explanation for this difference. The care model at St. Jude includes elimination of out of pocket costs for families and rigorous case management to ensure adequate treatment and follow-up (Pui et al., 2003; Bhatia, 2004); these factors may be particularly important for insuring optimal treatment in children from low income families. Care at St Jude also utilizes stringent risk stratification to ensure rapid identification and treatment of children at higher risk of relapse (Pui et al., 2003; Pui et al., 2018).

Implications for research:

The St Jude experience points to the need for development and evaluation of national strategies to provide equitable access to high quality healthcare and family support after a diagnosis of ALL (Table). Such efforts have the potential to resolve disparities in treatment outcome. However, additional questions about etiology, presentation, and treatment of ALL point to other important avenues of research.

Etiology and ALL disease sub-types

Epidemiological data suggest that a number of exposures contribute to ALL risk, including maternal smoking, alcohol intake and insufficient folic acid during pregnancy; prenatal and

postnatal exposure to pesticides, herbicides, paints and other chemicals, including air pollutants such as benzene; and postnatal radiation exposure (Timms et al., 2016; Shu et al., 1988; Whitworth et al., 2008; Van Maele-Fabry et al., 2019). Effects are generally small and no dominant or major contributors to risk have been identified (Schuz and Erdmann, 2016), suggesting that ALL may result from multiple exposures, potentially additive or interactive. Socioeconomic status (SES) has been evaluated as a risk factor with conflicting results. Some studies suggest that low SES is protective while others find no difference by SES (e.g., Ribiero et al., 2008; Adam et al., 2015; Smith et al., 2006). One study saw no effect of individual or residential SES but found that children from low income municipalities had a higher risk (Raaschou-Nielsen et al., 2004). SES or municipality characteristics could be a proxy for other exposures that are either harmful or protective. Some exposures (such as radiation and toxins) could result in mutagenesis or epigenetic changes promoting cancer development.

Inherited genetic variation also plays a role. Some genetic syndromes include ALL as part of their presentation; these conditions are rare and account for only a small proportion of ALL cases, but point to genes that are important in ALL etiology (Pui et al., 2018). In addition, variants in 21 genes have been associated with modestly increased or decreased risk of childhood leukemia; most of the genes are involved in the body's response to xenobiotic exposure, DNA repair, or cell cycle regulation. (Lim et al., 2014; Brisson et al., 2015). The lower incidence of ALL in AA compared to EA children can be partially accounted for by differences in prevalence of ALL risk variants (Lim et al., 2014), a finding consistent with the growing body of knowledge about differences in gene variant prevalence across different ancestral populations (Bustamante et al., 2011). Genetic characteristics of cancer cells also contribute to the definition of therapeutically relevant subtypes of ALL, including prognostic indicators and characteristics that influence treatment response (Pui et al., 2018). Might inherited susceptibility contribute to the higher rate of poor prognostic indicators in AA children? Or could differential exposure to environmental risk factors do so? Current data are insufficient to address these questions.

Implications for research:

A better understanding of factors contributing to ALL risk could lead to meaningful prevention opportunities (Schuz and Erdmann, 2016). One of the difficulties in interpreting the accumulating information about ALL risk is that different types of risk, such as those related to genetics or toxin exposure are typically studied separately, yet risk is likely the result of complex interactions or multistep causal pathways. Genetic susceptibility may influence an individual's response to exposures, so that some individuals are more vulnerable than others or react to exposures differently. Equally importantly, social factors may influence the likelihood, timing, or effect of different exposures. For example, AAs are more likely to live in areas where the level of toxic pollutants exceeds federally defined thresholds (Olden and White, 2005), a consequence of residential segregation that could influence how ALL presents in AA children. These observations point to the need for transdisciplinary collaboration to elucidate interactions among different contributing factors, including genetic predispositions, physical exposures, the social environment and genetic predispositions. Significant challenges include development of adequate methods for

determining and assessing exposures in utero and in early childhood and study designs with sufficient power to identify interactions (Table).

Treatment response

ALL treatment response varies among individuals within a given ALL sub-type (Pui et al., 2018). While many factors can influence drug response, including age, diet, co-morbidities and other concurrent treatments, pharmacogenetic differences play an important role in such interindividual variation (Wang et al., 2011). The earliest evidence of the significance of pharmacogenomics for ALL concerned response to thiopurines, a mainstay of ALL treatment. Thiopurines can result in serious, even life-threatening, effects on the bone marrow in some individuals. Retrospective analysis of clinical trial data showed that adverse effects of thiopurines are largely the result of genetic variation in the thiopurine S-methyltransferase (*TPMT*) gene (Relling et al., 2018; Relling et al., 1999). Individuals with a high risk *TPMT* genotype are particularly vulnerable to side effects of thiopurines; with knowledge of this susceptibility, physicians can use lower doses of the drug to avoid adverse outcomes, without a loss of efficacy in those sensitive to the drug's effects (Relling et al., 2006), and higher doses in those who can tolerate and benefit from increased exposure (Stanulla et al., 2005). More recent research into unexplained thiopurine intolerance in ALL patients documented that variation in the *NUDT15* gene also confers drug sensitivity (Moriyama et al., 2016; Moriyama et al., 2017). *NUDT15* catalyzes the conversion of TGTP to TGMP; a reduction in this activity leads to greater accumulation of "active" thioguanine nucleotides. Testing for *NUDT15* variation can further reduce thiopurine toxicity risk.

Although these findings represented an important advance in ALL treatment, they do not explain differences in treatment outcome between AA and EA children because the prevalence of *TPMT* risk genotypes is similar in both groups (Hon et al., 1999) and *NUDT15* risk allele frequencies are relatively low in both groups (Moriyama et al., 2017). However, other genetic studies of treatment response offer partial explanations for the observed racial disparities. A genetic profile associated with Central and South American indigenous ancestry predicts a higher relapse rate which can be resolved with an additional round of chemotherapy (Yang et al., 2011). This ancestry profile was seen primarily in Hispanic and EA children and could account for some of the reduced survival seen in Hispanic children.

Additional research points to a genetic contribution to AA relapse rates as well. A genome wide association study (GWAS) of a national sample of children with B-precursor ALL, a subset of the disease with poorer outcomes, identified several gene variants associated with relapse (Karol et al., 2017). Variants conferring increased risk of relapse were more common, and protective variants less common, in AA children. Two risk variants, in the *FARP2* and *RNASET2* genes, could account for most of the excess risk seen in AA children; two additional risk variants contributed significantly to relapse among Hispanic patients. The four variants were associated with a higher risk of relapse in all populations but were more prevalent in the AA and Hispanic populations respectively (Karol et al., 2017). Both of the variants associated with relapse among AA patients appear to affect treatment response. The

FRAP2 variant is associated with a reduced response to methotrexate. The *RNASET2* gene codes for an extracellular ribonuclease, with diminished activity in some ovarian tumors; it may have a role in tumor suppression (Acquati et al., 2005), but whether this finding is relevant to ALL relapse is unknown. However, the effect of the *RNASET2* risk variant was observed in only one of the two ALL protocols studied, suggesting that its effect varies with treatment regimen (Karol et al., 2017).

Implications for research:

Pharmacogenomic research related to ALL treatment provides guidance for improving ALL treatment (Pui et al., 2018) (Table). The identification of gene variants associated with adverse outcomes in B precursor ALL also provides an important insight into outcome disparities. Chemotherapy regimens optimized in predominantly EA populations may be less beneficial in other ancestral populations as a result of the differing prevalence of gene variants associated with treatment response. The outcome disparity for AA children, although explained in part by genetic differences, could thus reflect primarily that AA children constitute only a minority of the patient [population in which ALL treatments have been developed. As more diverse populations are studied, pharmacogenomic research can inform strategies for further improving risk-directed therapy, the model that has proved successful at St Jude Children's Research Hospital (Pui et al., 2003; Pui et al., 2018), and contribute to opportunities for equalizing treatment outcomes for children of all ancestral populations.

Conclusions

The ALL example points to a complex interaction between the social environment and genetics. Although health disparities occur as the result of social, environmental and economic disadvantages (Healthy People 2020), epigenetic, inherited and somatic genetic differences influence disease outcomes as well (Figure). The contribution of the social environment to ALL outcomes occurs through parental and early childhood risk exposure and through access (or barriers) to effective treatment. The genetic contribution occurs through inherited susceptibility to ALL, somatic genetic and epigenetic changes that contribute to carcinogenesis, and inherited differences in response to chemotherapy.

The health disparity between AA and EA children is, not surprisingly, also complex. AA children have a lower incidence of ALL, yet when they develop the disease, they present with higher risk profiles than EA children and experience higher relapse rates after treatment. The disparity in treatment response is in part due to genetic factors, but can be overcome with high quality treatment. In turn, high quality treatment involves both support for families and the use of genetic and other research to optimize treatment outcomes for all children.

The ALL example thus points to important ways in which precision health research can help to illuminate a health disparity and improve treatment, but also underscores the role of social factors in health outcomes. Arguably, the most urgent research for addressing ALL health disparities is health service and nursing science analysis focused on approaches that allow all children with ALL to benefit from effective care (Table). Yet, genomic and

pharmacogenomic research demonstrate that effective care requires understanding of population genetic differences that influence treatment response for different ALL disease sub-types.

A better understanding of the causal pathway for ALL – including why AA children have a lower incidence of ALL but a higher rate of poor prognostic indicators – could open new opportunities for prevention. As with treatment response, addressing this question will require the inclusion of diverse populations in research, with attention to both genetics and the implications of the social environment for differential risk exposure. Precision health research will contribute most fully to addressing cancer health disparities when it incorporates not only the power of genomic analysis but also a comprehensive assessment of the social and physical environment and the ways in which they contribute to complex disease pathways.

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Highlights

- African American children experience higher relapse rates after treatment for acute lymphoblastic leukemia than European American children.
- These differences were not seen at one center providing family support and high quality care, pointing to social factors as an important cause.
- However, differences in the prevalence of gene variants associated with treatment response also contribute to higher relapse rates among minority children
- Research on both social factors and genetic differences in treatment response are needed to ensure optimal care for children with ALL.

Figure. Cancer Health Disparities and Precision Health Research.

The ALL example illustrates the complex interplay between social determinants and genetics in cancer outcomes. Racial disparities in ALL outcomes can be largely accounted for by differences in access to effective treatment. Effective treatment in turn is informed by precision health research that includes study of inherited differences in treatment response. Further understanding of unexplained aspects of ALL in African American populations, including the lower incidence of the disease but higher rate of adverse prognostic indicators, will require both evaluation of differences in risk exposure and the contribution of epigenetics and inherited and somatic genetic variation to etiology and disease sub-types.

Table:**Opportunities for Research on Health Disparities in Acute Lymphocytic Leukemia (ALL)**

Topic	Research questions	Type of research
Access to care	How should optimal care for ALL be defined?	Health services; nursing science
	How can universal access be assured?	
Etiology	What risk factors contribute to ALL risk?	Epidemiology; environmental science; epigenetics; genetics
	What time frames influence risk?	
	Do risk factors interact or produce additive effects?	
	Do some population groups experience differential exposure to risk?	
Disease sub-types	What accounts for adverse prognostic factors in ALL presentation?	Epidemiology; environmental science; epigenetics; genetics
	Do some population groups experience differential exposure to risk?	
Treatment	What factors influence differences in treatment response across different population groups?	Health services; clinical oncology; genetics; pharmacogenomics; nursing science
	How can treatment response be equalized?	