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LETTER TO THE EDITOR

The Silent Crisis: Economic Burden of Genetic Disease Diagnosis in Low- and Middle-Income Countries (LMICs)

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Abstract

Genetic disorders, although secondary to infectious and non-communicable diseases in the global health priority agenda, are an important drain, albeit ill-defined, on the economies of low- and middle-income countries (LMICs) and on their health resources. The economic costs of diagnosing a genetic disorder in these settings, both direct and indirect, are detailed in the narrative review. Direct costs include the significant expense of advanced molecular diagnosis, inadequate infrastructure and dependence on expensive foreign services, which are largely financed through catastrophic, out-of-pocket payments. Indirect costs include the prolonged and expensive "diagnostic odyssey," the loss of productivity in patients and patients' relatives and the costs to society of misdiagnosis and avoidable disability. This emergency can be addressed by investing in strategic local diagnostic capacity, task-shifting and innovative finance models to enable equal access to genomic medicine and to break the vicious cycle of health-related poverty in LMICs.

Key words: Financial stress; Genetic diseases, inborn; Developing countries.

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The unrecognised burden

Genetic and rare diseases collectively affect millions of patients worldwide. However, their frequency is often underappreciated in low- and middle-income countries (LMICs) that lack a developed diagnostic infrastructure.[1] Although the focus in these regions is rightly on the infectious diseases and the common non-communicable diseases, the underlying genetic basis of many childhood and adult diseases accounts for a significant amount of the morbidity, mortality and disability.[2] The availability of next-generation sequencing (NGS) and associated technologies at relatively affordable costs heralded a revolution in diagnostic medicine. This has generally bypassed LMICs so far; hence, gross diagnostic disparity exists.[3] The economic implications for LMICs of the diagnosis of these disease processes are manifold, in that they bear an economic burden both on national health spending and on individual households and at times forcing them into poverty. This review is designed to systematically investigate the direct and indirect economic effects of the genetic diagnostic deficit in LMICs.

The diagnostic disparity in LMICs

Prevalence and clinical presentation

Contrary to popular belief, genetic abnormalities are not uncommon in LMICs. High consanguineous marriage rates in particular populations, coupled with a dwindling rate of infectious disease deaths, have served to elevate the relative importance of hereditary diseases to child morbidity.[4] Sickle cell disease, thalassemia and several inborn errors of metabolism (IEM) will be among the most pressing public health problems. The lack of organic newborn screening facilities results in most diagnoses of such conditions not being made until considerable time has elapsed, when severe and generally irreversible clinical manifestations have been supervised.[5]

The diagnostic odyssey and its cost

The processes involved in arriving at the diagnosis of a genetic disease in LMICs are generally a protracted and very expensive "odyssey". Over several years, patients spend vast sums of money consulting many specialists and being treated for wrong or "unassignable" diagnoses.[6] Illustrative direct costs incurred on the odyssey:

- Repeated non-specific testing: Expenses incurred in unnecessary imaging, biopsy and blood examinations to exclude common disorders.
- Transport and accommodation: Many successive journeys frequently across long distances before they can reach the tertiary referral centre in the capital, with a consequent drain on personal family resources.[7]
- Loss of wages lost on the journeys of transport: Caregivers (usually the mother in LMIC) have to give up work or subsistence agricultural duties, resulting in immediate economic loss.[8] This delay in arriving at a correct diagnosis is due to the absence of locally available, combined and appropriate testing, which results in poorer clinical outcomes and significantly greater accumulated economic costs of treatment than when an early, correct diagnosis can be made.[9]

Direct economic burden of diagnosis

The direct economic burden is due to the high cost of technology, reagents and infrastructure for definitive genetic diagnosis.

Cost of molecular diagnostics

Globally, sequencing costs have decreased but remain inordinate within LMIC health systems. A single whole exome sequence (WES) is often required for many complex paediatric presentations and costs several hundred to over a thousand US dollars (USD). This expenditure alone to test these individuals is often more than the annual per capita health expenditure in many LMICs.[2]

The fiscal implications of molecular diagnostic tests include:

- Capital expenditure: For purchasing and maintaining high-throughput sequencers, which require a stable power supply, climate control and uninterrupted supply chains.[6]
- Reagents and consumables: Seldom produced locally, these are commonly imported and subject to high tariffs, requiring specially controlled cold-chain logistics. As a result of this combination, reactants significantly increase the per-test costs.[3]
- External costs: Where local testing is not available, samples are sent to either a high-income country (HIC). The added costs, including shipping, laboratory processing and administration, make these tests economically inaccessible to all but the wealthiest families.[1]

Human resource and infrastructure deficiencies

The economic burden is not only confined to the costs of equipment. A crucial bottleneck is the availability of a trained workforce, such as clinical geneticists, genetic counsellors and bioinformaticians.[10]

- Cost of training: Training these specialists often involves expensive international fellowships or training programs and thus is a considerable capital investment for the government or university.[9]
- Retention: Severe brains drain of highly trained genomic specialists to HICs or the private sector often leads to the training cost and poor return on investment.[4]

- Data analysis: The cost of bioinformatics analysis, the highly skilled commodity that is required to make sense of sequencing data, often exceeds the cost of the sequencing procedure itself, especially when subscription analysis and other computing services require payment.[9]

Financing of genetic testing and out-of-pocket (OOP) costs

In many LMICs, universal health coverage schemes do not exist, or advanced genetic diagnostics are excluded.[3] Therefore, the direct costs of diagnosis are borne, for the most part, by OOP expenditure by the patient's family. OOP expenses for one genetic diagnosis are a significant reason for catastrophic health expenditure.[5] This expenditure causes families to liquidate assets, incur debts at usury rates, or choose between pursuing a diagnosis and meeting basic expenses, thereby deepening the poverty trap.[6]

Indirect economic burden and social costs

Economic burdens incurred from the indirect effects of undiagnosed genetic disorders vastly exceed direct healthcare costs and play out in the areas of productivity, social capital and strain on the healthcare system.

Productivity loss and caregiver burden

Genetic diseases in children require extensive and continual supervision and care. The burden of care primarily falls on the primary caregiver, which prevents them from fully participating in the formal or informal labour force.[1]

- Caregiver productivity loss: The continual care needs attendant to clinical visits, hospitalisations and home care result in lost earnings, loss of retirement savings and educational loss to the caregiver, thus working to the detrimental effect on the future economic status of the next generation.[9]
- Patient productivity loss: Such situations as the delayed or missed diagnosis intermediate to the progress of the disease often lead to irreversible physical or mental handicap to the patient, which tends to lessen future employability and contribution to the labour force and national economy for the patient's lifetime.[4]

Strain on the healthcare system and cost of misdiagnosis

Without the available diagnostic abilities, healthcare systems are unduly forced to assume costs to manage symptoms of the diagnosed disease, often employing inappropriate treatments.[9]

- Unwarranted admissions: Patients with undiagnosed IEMs, for example, may suffer repeated metabolic crises leading to exorbitant and wasted admissions to the expensive intensive care unit (ICU), which deprives others of the use of the valuable resources present in the hospital.[5]
- Wasteful procedures: Incorrect diagnoses lead to the misplaced prescription of expensive, unnecessary, or even harmful drugs, which is a waste of hard-to-come-by budgetary resources in health care and may ultimately lead to speeding the pace at which the disease progresses.[10]

Social and psychosocial costs

Although more challenging to quantify, the social costs of disease have a profound impact on the long-term economic viability. These costs include:

- Stigma and discrimination: There exists a social stigma affecting genetic diseases, with consequent discrimination in education, employment and marriage. This negatively influences economic mobility.[6]
- Mental health costs: The ongoing stress, financial insecurity and bereavement resulting from an extended diagnostic odyssey and in the management of a complex disease, result in high degrees of anxiety and depression among caregivers, thus increasing the burden on scarce mental health services, which are usually rudimentary in low and middle-income countries.[3]

Policy interventions and mitigating the burden

Genomic medicine should now be incorporated into health policies. Governments must define ethical and (legal) parameters under which the genetic data is stored, or how privacy is evoked, or looked at when used for clinical matters.[3] With

a good policy, we can attract research funding and secure the local expertise needed, among other benefits. This could mean transforming something that requires additional funding into something that generates more value from the economic perspective, ie, necessitating education of the population, development of the elite and so on.[6]

Diagnosing the inequity imperative

If gene defects affect many people worldwide, the availability of definitive diagnoses is heavily skewed towards the high-income countries (HICs).[2] The odyssey of diagnosis for these patients in the LMICs often turns out to be financially and emotionally expensive, lasting for years and devastating family and public health budgets, with no result. The major problem is that the costs of technology are prohibitive. Although the cost of sequencing the whole human genome (whole genome sequencing, WGS) is now very low, the actual clinical costs, including preparations (sample), sequencing reagents, bioinformatic analyses, interpretations and professional costs, can still run between $5,000 and over $10,000 per patient.[11] Such costs are incompatible with the per capita health expenditure in many countries and the basic needs for the things required for the maximal efficiency of health delivery systems pose an economic burden that impedes equitable health service provision. Additionally, the lack of a suitable genetic registry in LMIC countries is a significant source of economic inefficiency. Such registers enable the collation of data on local disease prevalence, the common pathogenic variants responsible and the development of targeted and fewer, therefore more cost-effective, gene panels. Without this basic database, activities by clinicians can only result in a choice between the prohibitively high costs of the "shotgun" method of genetic investigation by WGS or whole exome sequencing (WES) or symptomatic treatment, so involving significant opportunity costs and wasted resources.[12]

The rising expenses of advanced genetic diagnosis

The advanced science of genetic diagnosis is dominated by a few methods, each relatively distinct in terms of cost and complexity. Understanding these diagnostic costs is important if an economic method is to be established. Next-generation sequencing (NGS) and whole-genome sequencing (WGS). The most excellent throughput and cost. The cost of raw sequencing amounts to a few hundred dollars, while the clinical price remains high (approximately $4,000 to $8,000+) due to necessary infrastructural means and primarily through the interpretative and labour-intensive bioinformatic and clinical costs of analysing such a large data set.

WES involves the (exome) sequencing of the protein-coding area of approximately 1–2 % of the genome, accounting for well over 85 % of the known disease-producing mutations.[13] WES is typically around half the price of WGS and the standard clinical cost ranges from $1,500 to $4,000. In fact, for many rare diseases, WES is the clinically accepted gold standard, yielding a significant diagnosis rate (25—40 %) at a relatively low cost compared to WGS. Gene panels (targeted sequencing) is NGS used to examine specific genes associated with a particular condition, such as myopathy or intellectual deficit. The price of the gene panels ranges from $500 to $1,500. The method is only very effective when, upon clinical examination, the patient's observable phenotype (characteristic traits and/or symptoms of disease) is closely linked to a known set of genes.

Traditional and molecular methods

- Karyotype and fluorescence in situ hybridisation (FISH): These traditional methods detect high-level chromosomal structural variations and aneuploidies. They are inexpensive, costing $100 to $300 for a test. Although the diagnostic yield is unsuitable for most single-gene disorders, they help identify common chromosomal diseases. They are also an important and very cost-effective tier 1 screening tool.
- Sanger sequencing (single gene test): The gold standard for confirmation of a single known mutation or for testing a single gene if the phenotype is totally diagnostic, which it often is, costing $50 to $150, it is the lowest cost form of sequencing, but is only diagnostically practical if the diagnosis is almost determined.

- Multiplex ligation-dependent probe amplification (MLPA): A powerful, cheap test for detecting minor copy number variations (deletions or duplications) in specific genes. MLPA panels are inexpensive, typically costing less than $200 and can occasionally replace the more expensive array-based comparative genomic hybridisation.14

The LMIC context: Registry gap and infrastructure strain

The financial burden of GD disease in LMICs is compounded by a double systemic problem in infrastructure and an absent registry. Firstly, the infrastructure in LMICs usually lacks high-throughput sequencing machines, a stable power supply and a continuous supply chain of reagents. Even if this capital cost is met from grants, the day-to-day running costs are often unsustainable. Most critical is an acute shortage of locally trained bioinformaticians and genetic counsellors, who are essential for interpreting WES and WGS data.
Secondly, the lack of a viable national or regional patient registry means that clinicians do not have adequate epidemiological information. In HICs, large registries (such as the *UK Biobank* or centralised health records) enable the design of tailored gene panels, ensuring that the most common mutations in a region are included. This results in an increased diagnostic yield and more cost-effective testing. In the absence of a registry, there is no local, reliable information to enable the adequate design of a gene panel; hence, the only option is to use generic patient gene panels, which are internationally oriented. This could lead to loss of regionally new or rare variants or mutations and further provisions of unnecessary repeat tests, resulting in financial wastage.[15]

Advising on the cheapest and most feasible strategies

To enable genomics to be economical and attainable in countries lacking registries and associated support, a practical, flexible, tiered approach to diagnostics is required that, as far as possible, aims to maximise the unit cost of diagnosis. With this strategy, expensive WES/WGS technologies should not be used unnecessarily as a first-line approach.

Tier 1: Low-cost primary screening (the foundation)

The most cost-effective yet reliable strategy is to begin with non-NGS technologies and accurate clinical filtering.

- Rigid phenotype-based triage: The first and crucially cost-effective aspect is an exacting clinical examination of the patient and family tree. A particular phenotype may warrant, first, a single, inexpensive test.
- Karyotyping, MLPA: All cases presenting with syndromic or microdeletion disease will be subjected to karyotyping or MLPA panels. They have a very high sensitivity for all significant structural alterations, but are easily obtained and inexpensive to perform; they require minimal bioinformatic input.
- Sanger sequencing: Utilised only as a diagnostic confirmatory method when the clinical picture strongly suggests a monogenic disease (for example, Duchenne muscular dystrophy) or when a common regional mutation has previously been identified by small-scale research.

Tier 2: The inexpensive passenger (targeted NGS)

This is the most economical option for advanced investigations when Tier 1 is negative, specifically gene panels.

- Custom regional gene panels: It is essential to partner with international partners or research institutions to consider the identification of the 100–200 commonest genetic diseases in the local population. A custom-designed gene study for these diseases alone would offer the best compromise of cost (approximately $1,500) and yield (over 25 %) compared with readily available international studies.
- Pooled sequencing (reduction in costs): Regarding diminishing reagent costs to the LMIC laboratories, pooling strategies may be adopted. The DNA samples from several individuals can be physically pooled and sequenced in a single NGS flow cell. This would require demultiplexing and individual analysis, but it would significantly reduce per-sample reagent costs and mathematically, it could be much cheaper overall.16

Tier 3: Selective advanced investigation (outsourcing)

Only such patients should be eligible for WES/WGS when undiagnosed after sectors I and II, particularly when they experience complex non-syndromic, highly unusual presentations.

- Outsourcing and partnership: LMIC should not purchase and maintain local infrastructure of WES/WGS but rather concentrate on outsourcing the sequencing and complex bioinformatic analysis to local HIC facilities or global humanitarian sequencing programs.17 The LMIC facility would perform only sample preparation and sending, significantly releasing local infrastructure pressures and costs.
- Shifting focus: Local capital should shift from sequencing hardware to training genetic counselling and interpretation specialists who can accurately interpret the returned WES data, thereby realising the full value of the data without the unnecessary overhead of the sequencing pipeline itself.

The road to economic genetic diagnosis in LMIC nations is not paved by the adoption of WGS machines, but rather by embracing selective, staggered and affordable technologies. The financial burden of adopting HIC diagnostic standards nationwide will be unsustainable. By prioritising fine clinical triage (Tier 1), utilising cheap gene panels and pooling strategies (Tier 2) and saving WES/WGS outsourced for only the most complex cases (Tier 3), LMIC nations can achieve a respectable diagnostic yield while in abject poverty. Closing the "registry gap" through tailored data collection and international cooperation remains the ultimate goal for creating truly optimised and affordable genetic healthcare systems.

Conclusion

The economic front, without going into the politics and so on, could make the burden of just diagnosis suffer in these LMIC, big trouble, (the effect of) poverty and inequality is accepted. The damage caused by the cumulative costs of the odyssey involved in the diagnosis, the excess price of imported technology and the work and productivity lost, is infinitely too high compared to the money needed to establish a strong local diagnostic base. The international health bodies, the countries that are LMICs and the private side of partners needed for any medical system must accept that genetic diagnostics is really a luxury, instead of a beginning element that is a vital part of the equitable health system, also a sort of strategic thing that is an economic necessity, so to speak. Investing in genomic capacity is equivalent to investing in human capital, leading to earlier intervention, reduced disability, lower long-term healthcare expenditures and increased societal productivity.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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