Rare Expertise

WHITE PAPER

# The Future of Genetic Testing in the Diagnosis of Rare Diseases

Reducing the Diagnostic Journey.
Eliminating Unnecessary Treatments.
Delivering Cost Savings.

**A Rare Expertise White Paper**

For rare disease marketing and medical affairs professionals

rareexpertise.com

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SECTION 01

# Executive Summary

Rare diseases affect an estimated 300 million people worldwide, yet the path to an accurate diagnosis remains one of medicine's most protracted and costly challenges. Patients endure an average of 4 to 8 years on a diagnostic odyssey — a journey marked by repeated misdiagnoses, empirical treatment trials, and significant personal and financial burden.

Advances in genetic testing — particularly next-generation sequencing (NGS), whole exome sequencing (WES), and whole genome sequencing (WGS) — are fundamentally reshaping this landscape. Combined with artificial intelligence-assisted phenotyping, expanded newborn screening programs, and rapid genomic analysis platforms, these technologies offer a transformative opportunity: dramatically shortening the time to accurate diagnosis, eliminating years of unnecessary and potentially harmful treatments, and delivering measurable cost savings to patients and health systems alike.

**300**M
people worldwide
LIVING WITH A RARE DISEASE

**4–8**yrs
diagnostic odyssey
AVERAGE LENGTH

**80**%
genetic origin
OF RARE DISEASES WITH KNOWN CAUSE

This white paper sets out the current state of genetic testing in rare disease diagnosis, the technologies driving change, and the compelling clinical and economic case for their broader adoption.

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For too long, patients with rare genetic diseases have navigated a fragmented healthcare system alone, often spending years searching for answers. Genomic medicine has the potential to change that — not incrementally, but ***fundamentally***.

FRANCIS COLLINS, MD, PHD — FORMER DIRECTOR, NATIONAL INSTITUTES OF HEALTH

SECTION 02

## Background: The Rare Disease Diagnostic Challenge

A disease is typically classified as 'rare' when it affects fewer than 1 in 2,000 people. Yet there are over 7,000 known rare diseases, meaning that collectively they affect a substantial proportion of the global population. Approximately 80% of rare diseases have a genetic origin, making them in principle amenable to diagnosis through genetic testing.

In practice, however, genetic testing has historically been a last resort rather than a first-line tool. Clinicians typically exhaust conventional investigations before ordering genetic panels, and access to specialist genomic medicine services remains uneven across healthcare systems. The result is a diagnostic odyssey that imposes immense burdens on patients, families, and health systems alike.

> KEY PROBLEM
>
> During this period, patients are often subjected to treatments targeting the wrong condition, some of which carry significant risks of harm. Families face uncertainty, emotional distress, and in many cases substantial out-of-pocket costs. Health systems absorb the expense of repeated consultations, investigations, and hospital admissions — without delivering clinical value.

SECTION 03

## Shortening the Diagnostic Journey

The most immediate clinical impact of modern genetic testing is the potential to compress the diagnostic odyssey from years to weeks — or, in some settings, to days. Several converging technologies are driving this shift.

## Next-Generation Sequencing

Traditional genetic testing examined individual genes or small panels relevant to a suspected diagnosis. Next-generation sequencing allows the simultaneous analysis of millions of genetic variants across the entire genome. Whole exome sequencing interrogates the protein-coding regions of all genes — the area responsible for most known rare disease mutations — while whole genome sequencing extends analysis to the non-coding regions as well.

| 25–50% | <24hrs |
| --- | --- |
| **diagnostic yield** | **turnaround time** |
| OF WGS/WES IN PREVIOUSLY UNDIAGNOSED PATIENTS | RAPID WGS IN NEONATAL ICU SETTINGS |

In clinical studies, diagnostic yields of 25–50% have been reported for patients who had previously gone undiagnosed through conventional testing, representing a transformative improvement in diagnostic capability.

## Rapid Genomic Sequencing in Critical Settings

In neonatal intensive care units, rapid whole genome sequencing has demonstrated turnaround times of under 24 hours in critically ill infants. What previously took months — or went entirely unresolved — can now be diagnosed within days of admission. This capability is particularly important in neonates, where early diagnosis can determine whether a targeted therapy exists, guide surgical decisions, or inform palliative care planning.

> *When we can sequence a critically ill infant's genome in 24 hours and identify an actionable diagnosis, we have crossed a threshold. The question is no longer whether genomics belongs in the ICU — it's why we waited so long.*
>
> Stephen Kingsmore, MD, DSc — President and CEO, Rady Children's Institute for Genomic Medicine

## AI-Assisted Phenotyping

Artificial intelligence tools are emerging as powerful enablers at the front end of the diagnostic pathway. Natural language processing platforms can mine clinical notes and electronic health records to identify patients with symptom patterns consistent with rare genetic conditions, flagging them for earlier referral to genomic medicine services.

Facial recognition software trained on dysmorphic features — physical characteristics associated with specific genetic syndromes — can suggest candidate diagnoses from photographs, offering clinicians a rapid, low-cost initial triage tool. These technologies do not replace clinical judgment but amplify the ability of generalist clinicians to recognize rare disease patterns they may encounter infrequently.

## Expanded Newborn Screening

Traditional newborn bloodspot screening has identified 50 to 60 metabolic conditions since its introduction in the 1960s. Genomic newborn screening programs, now being piloted in several countries, extend this to hundreds of actionable conditions — identifying affected children before symptoms emerge and enabling pre-symptomatic treatment that can prevent irreversible harm.

> THE TRAJECTORY
>
> As sequencing costs continue to fall — now approaching $200 per genome — the economic case for population-level newborn genomic screening is strengthening. The trajectory is clear: genetic testing is transitioning from a last resort to a first-line diagnostic tool.

# $50K–$150K

Estimated average cost of the diagnostic journey before a correct rare disease diagnosis is reached — a figure that dwarfs the cost of a comprehensive genomic test.

THE MOST EXPENSIVE TEST IN RARE DISEASE IS THE ONE YOU DIDN'T ORDER.

SECTION 04

# Cost Savings: Eliminating Unnecessary and Incorrect Treatments

The financial argument for early genetic diagnosis is compelling, and consistently underestimated by health systems that consider only the upfront cost of the test. A full accounting of costs — incorporating downstream savings from avoided investigations, incorrect treatments, and preventable hospitalizations — consistently demonstrates strong net value.

## The True Cost of Diagnostic Delay

A patient who spends five years on the diagnostic odyssey accumulates substantial costs through repeated imaging, specialist consultations, laboratory investigations, empirical drug trials, and hospitalizations. Studies have estimated the average cost of the diagnostic journey for a rare disease patient at between $50,000 and $150,000 before a correct diagnosis is reached — a figure that dwarfs the cost of a comprehensive genomic test.

Beyond direct financial costs, delayed diagnosis results in lost productivity, increased carer burden, and in many conditions, irreversible disease progression that creates long-term care needs which would not have arisen with earlier intervention.

## The Harm and Cost of Incorrect Treatments

Misdiagnosis does not merely delay appropriate treatment — it frequently results in active harm. A child with a mitochondrial disorder misdiagnosed as an epilepsy syndrome may receive valproate, a drug that is not only ineffective but specifically contraindicated in mitochondrial disease and capable of precipitating serious, potentially life-threatening deterioration. The cost of managing drug-induced complications, in addition to ongoing ineffective treatment, significantly compounds the financial and clinical burden.

> *The most expensive test in rare disease is the one you didn't order. The cost of diagnostic delay — in suffering, in wrong treatments, in irreversible disease progression — dwarfs the cost of genomic testing many times over.*
>
> David Dimmock, MD — Chief Medical Officer, Rady Children's Institute for Genomic Medicine

## Precision Treatment and Rational Resource Allocation

For a growing number of rare genetic diseases, accurate diagnosis unlocks access to highly targeted therapies — enzyme replacement therapies, gene therapies, RNA-targeted treatments, and specific small molecules — that are only effective in patients with the confirmed genetic cause. These treatments are frequently among the most expensive in medicine.

Directing these therapies only to patients with a confirmed genetic indication, rather than trialing them empirically across a broader population, represents both better medicine and more rational resource use. Health technology assessment bodies increasingly require molecular diagnosis as a prerequisite for reimbursement, making genetic diagnosis an enabling step in access to treatment.

## Health Economic Evidence

Health economic modeling consistently demonstrates that earlier genomic testing — accounting for the full cost of the test — results in net cost savings when downstream reductions in unnecessary procedures, incorrect treatments, and avoidable hospitalizations are factored in.

**$14K**
average saving per patient
RAPID WGS IN NEONATAL ICU VS STANDARD WORKUP

**<12mo**
break-even point
EARLY GENOMIC TESTING VS COST OF AVOIDED UNNECESSARY CARE

**~$200**
per genome
CURRENT SEQUENCING COST AND FALLING

A 2022 analysis of rapid whole genome sequencing in critically ill infants found a cost saving of approximately $14,000 per patient compared to standard diagnostic workup, driven primarily by reduced length of stay and avoided investigations. As testing becomes faster and less expensive, this economic case will only strengthen.

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We are entering an era in which a child's entire genome can be read at birth, diseases identified before symptoms emerge, and treatments started in the window when they will do the most good. The obstacle is no longer the science — ***it is the will to deploy it***.

SHARON PLON, MD, PHD — PROFESSOR OF PEDIATRICS AND MOLECULAR & HUMAN GENETICS, BAYLOR COLLEGE OF MEDICINE

SECTION 05

# Recommendations

Based on the evidence reviewed in this paper, we make the following recommendations for health systems, commissioners, and clinical leaders:

### 1. Integrate genetic testing earlier in the diagnostic pathway

Integrate genetic testing — including NGS panels and exome sequencing — earlier in the diagnostic pathway for patients with suspected rare disease, rather than as a last resort after exhausting conventional investigations.

### 2. Commission rapid whole genome sequencing for critically ill neonates

Commission rapid whole genome sequencing services for critically ill neonates and children as a standard-of-care offering, supported by clear clinical pathways and multidisciplinary genomic interpretation infrastructure.

### 3. Invest in AI-assisted phenotyping tools

Invest in AI-assisted phenotyping tools to support generalist clinicians in identifying rare disease patients earlier and routing them efficiently to specialist services.

### 4. Develop and expand newborn genomic screening pilots

Develop and expand newborn genomic screening pilots with robust outcome monitoring, informed by health economic modeling of population-level benefit.

### 5. Adopt comprehensive health economic frameworks

Adopt health economic frameworks that capture the full value of early genetic diagnosis — including downstream savings from avoided unnecessary treatment — when evaluating the cost-effectiveness of genomic medicine investments.

### 6. Ensure equitable access to genetic testing services

Ensure equitable access to genetic testing services across patient populations, addressing geographic, socioeconomic, and ethnic disparities in current referral patterns.

SECTION 06

# Conclusion

The convergence of falling sequencing costs, AI-enabled phenotyping, and expanding clinical evidence is creating a once-in-a-generation opportunity to transform the diagnosis of rare diseases. The technology now exists to end the diagnostic odyssey for many patients — replacing years of uncertainty, misdiagnosis, and harmful incorrect treatment with an accurate genetic diagnosis achievable within days.

The clinical case is clear. The economic case is equally strong. What remains is the commitment from health systems, payers, and clinical leaders to embed genetic testing at the front of the diagnostic pathway — not its end.

For the 300 million people living with a rare disease, many of them children, that commitment cannot come soon enough.

*For further information, please contact the authors of this white paper.*

# Rare Expertise

Rare Expertise is a strategic consultancy focused on helping companies developing and marketing products for patients with rare diseases. Our mission is to shorten the diagnostic and treatment journey in people with rare diseases through better education.

Rare Expertise and the Rare Medical Network work at the intersection of rare disease knowledge, clinical practice, and trusted professional networks. Our focus is on supporting healthcare professionals with credible information and access to expertise — when it matters most.

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