Doubling Diagnostic Yield with DISGENET

Introducing Dr. Massimiliano Chetta: Principal Investigator & Senior Geneticist

Dr. Massimiliano Chetta and his team at A.O.R.N. Cardarelli Hospital in Naples, Italy, **dramatically increased its diagnostic yield—from 35% to 80–85%—by embedding DISGENET into its clinical exome sequencing workflow.** This represents not only an increase in detection rate but also a fundamental change in diagnostic methodology, transitioning from phenotype-limited searches to data-driven gene-disease network interrogation.

> *Now we have a detection rate of 80–85%. Using DISGENET, I give the medical doctor answers they didn't expect—sometimes changing the diagnosis completely.*
>
> ***-Dr. Chetta***

By shifting to a multi-gene approach and using DISGENET's rich gene- and variant-disease association data, Dr. Chetta and his team have **accelerated diagnosis, uncovered hidden disease associations, and provided clinicians with faster, more confident answers for patients and families.** This adoption illustrates the shift from symptom-based, descriptive medicine to data-driven, mechanistic interpretation of genomic variation.

Challenges

Despite advances in next-generation sequencing (NGS), Dr. Chetta's team faced a significant bottleneck: a low diagnostic rate when using traditional Clinical Exome Sequencing (CES) pipelines. Standard phenotype-first strategies, relying on tools like HPO (Human Phenotype Ontology) and OMIM, often fell short—especially for disorders marked by high genetic and allelic diversity, where multiple genes may contribute to the condition.

In addition, most variants identified through CES were classified as variants of uncertain significance (VUS), offering little clinical value. Inconsistencies across variant annotation databases further reduced confidence in results. Together, these limitations left many patients undiagnosed despite extensive sequencing.

Recognizing the urgency, Cardarelli Hospital sought a more powerful approach to transform complex genomic data into clear, actionable diagnoses. The central challenge was not generating more sequencing data, but the extraction of clinically relevant meaning from existing datasets.

The Solution: Introducing DISGENET

To break through this limitation, the lab implemented a multi-gene strategy. Using this approach, they can evaluate all potential genes that may contribute to a condition. The genes harboring variants in each patient were selected, and then were prioritized using DISGENET information.

> *We switched to a 'reverse genomics' approach, filtering the gene list from clinical exome sequencing, then using DISGENET to enrich it for specific characteristics, like disease associations or clinical traits.*
>
> ***-Dr. Chetta***

This shift constitutes an inversion of the traditional workflow: rather than beginning with phenotype-driven candidate gene selection, the team applies data-driven gene prioritization enriched with gene-disease association information.

The result: a fundamental shift in how diagnoses are approached and resolved.

Results

Faster, More Confident Diagnoses

By embedding DISGENET into the workflow, the team increased the diagnostic yield from 35% to 80–85%.

Beyond the increase in yield, the key outcome is a substantial reduction in diagnostic uncertainty, with implications for both clinical decision-making and health system efficiency.

Key Case: Redefining Cataract Diagnosis

> *In one case, the initial diagnosis was just an eye problem, but with DISGENET I found a pathogenic variant linked to cataract. That completely changed the diagnosis.*
>
> ***-Dr. Chetta***

This demonstrates how disease entities previously categorized as isolated, organ-specific disorders can, through molecular evidence, be reframed as manifestations of broader systemic or genetic syndromes.

Key case: Complex Genetic Conditions

A published study at Cardarelli Hospital in Naples analyzed 32 patients with complex genetic diseases. These conditions were characterized by significant phenotypic variability, presenting challenges in clinical interpretation and diagnosis.

The suspected diagnoses were:

- Autoinflammation / Immune dysregulation (20 patients)
- Hemolytic Uremic Syndrome (9 patients)
- Waldenström Macroglobulinemia (3 patients)

Clinical exome sequencing was performed, but using standard approaches, no pathogenic variants were identified in any of the three WM patients or in 7 of 9 HUS patients.

By leveraging DISGENET's advanced NLP, a significantly larger pool of gene matches was revealed—**raising the diagnostic yield from 16 cases to all 32 cases.**

This demonstrates the capacity of advanced NLP approaches. Not only to increase diagnostic resolution but also to expand the scope of genotype-phenotype associations captured during clinical evaluation.

As well as solving previously undiagnosed cases, DISGENET data provided additional insights. In the WM group, different genetic variants in disease-associated genes were uncovered, enabling the reassessment of patients' diagnoses.

In one HUS patient, the diagnosis was refined, confirming the presence of the NLRP1 variant c.3589C>A, associated with an increased risk of Addison's disease, which can lead to renal microangiopathy and, eventually, renal failure.

This illustrates how network-level genetic interrogation can reveal comorbid risk associations, positioning diagnosis not as a terminal event but as a dynamic, continuously updated clinical construct.

Why DISGENET?

When evaluating tools to enhance diagnostic yield, the Cardarelli team looked for a platform that could:

- Support their multi-gene approach
- Prioritize gene–disease associations with clear scoring
- Provide direct links to literature for fast validation
- Provide mechanistic insights into the variability of clinical manifestations, offering important information on the landscape of complex genetic conditions.

DISGENET was selected because it enables systematic integration of genomic variants with curated disease associations. It bridges the gap between genotype and clinical phenotype through mechanistic interpretability.

Transforming Diagnostics With DISGENET

By embedding DISGENET into the diagnostic workflow, Dr. Chetta has more than doubled the diagnostic yield. **The result: faster, more accurate, and actionable insights that directly improve patient care.**

More significantly, this case demonstrates that the integration of gene–disease associations redefines diagnosis as a process of dynamic genomic interpretation rather than static categorical assignment.

This case also illustrates how DISGENET can transform disease diagnosis. DISGENET helps turn complex genomic data into clear answers for doctors and, more importantly, for patients and their families.

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