

How Nature's Randomized Clinical Trial Can Inform Yours



Only 10% of candidate therapies in chronic diseases that enter clinical trials are eventually approved by the Food and Drug Administration (Sun et al. 2022). Many of these failures can be traced to the earliest stages of drug discovery, particularly the selection of biological targets that later prove to be less effective or more toxic than anticipated (FIG 1).

Late-stage clinical failures are often driven by our inability to predict effects in humans. By the time that uncertainty is resolved, enormous amounts of capital—and years of effort—have already been committed (FIG 2). This forces you to make critical

decisions today—where to invest, which indications to pursue — knowing the truth won't be revealed until years later. And that's fundamentally broken: patients should not bear the cost of uncertainty in drug development when we have the means to reduce it.

“You have to decide today what will only be proven right or wrong years from now.”

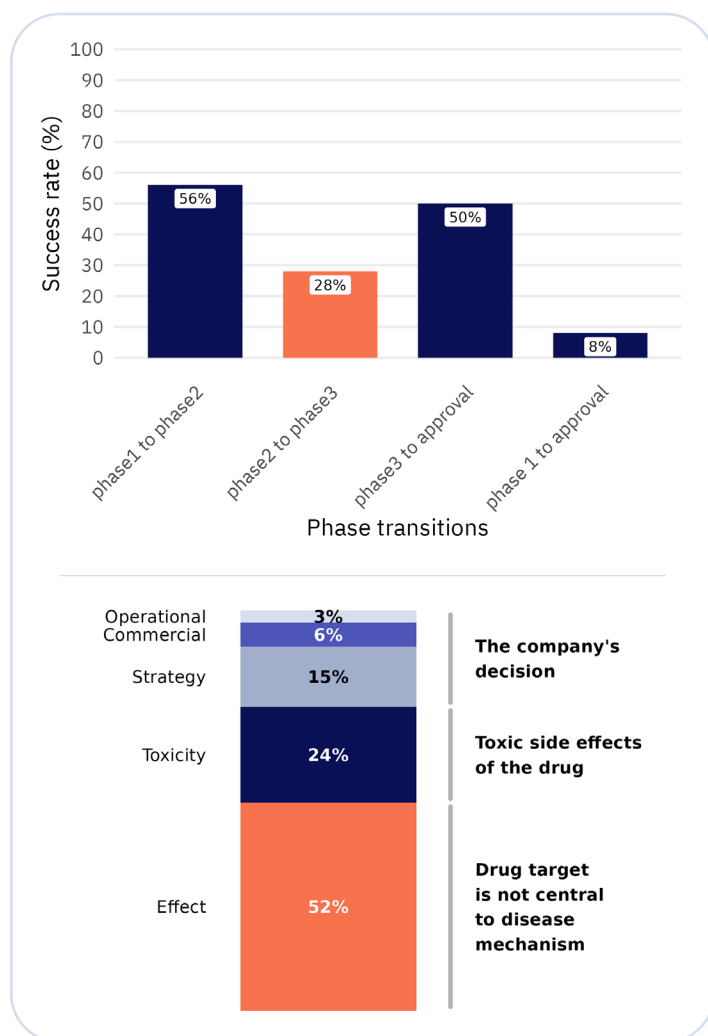


FIG 1. The highest rate of failures occurs in phase 2 trial where efficacy signal is tested in humans for the first time. Accordingly, the most common reason for failure is a lack of drug efficacy, which accounts for 55% of terminated clinical trials. Safety issues are not far behind (Dowden and Munro 2019).

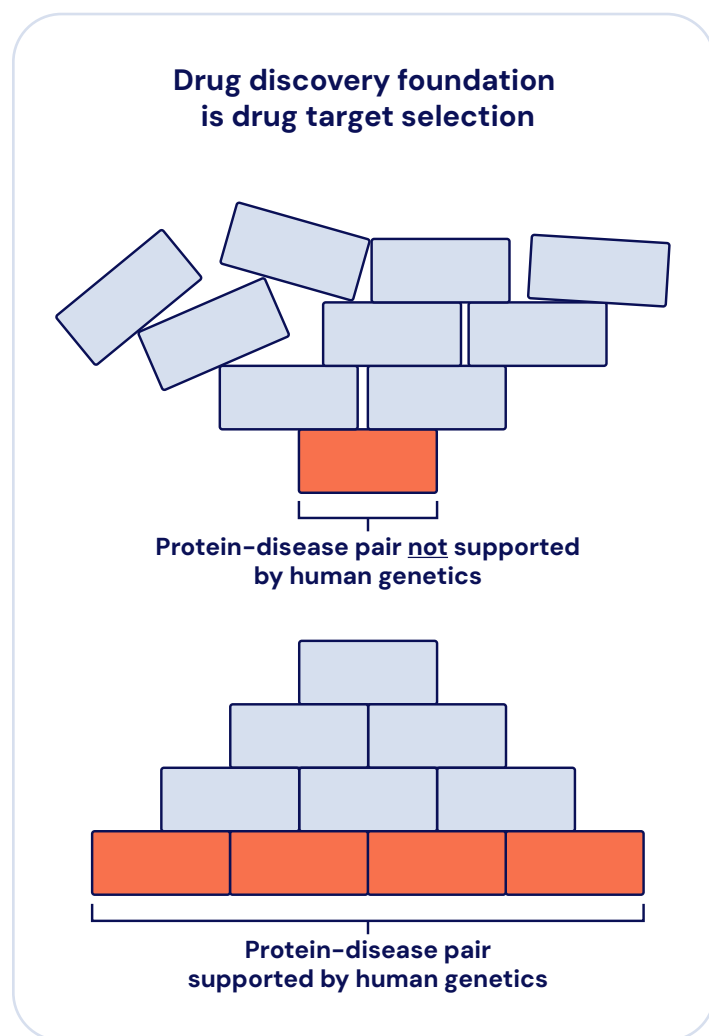


FIG 2. Drug discovery Foundation is target-indication selection. Selecting a target that is not central in the disease pathophysiology means that the drug program is doomed to fail from the start.

Naturally occurring genetic variation in the human population can be used to predict drug target effects in humans. Because germline genetic variants are inherited at conception and are generally stable over time, they cannot be modified by the development of a disease, thereby eliminating reverse causality bias. Furthermore, because germline genetic variants are inherited randomly at conception, they are largely independent of environmental and lifestyle confounding factors. For example, a patient's body mass index in adulthood does not influence the variant they carry at any genomic location. In essence, studying naturally occurring human genetics in the population is akin to leverage Nature's randomized clinical trial to predict the outcome of a real one (FIG 3).

Drug target indication pairs supported by human genetics are 2.6 times more likely to receive FDA approval compared to target indication pairs without such support (Minikel et al. 2024).

Target validation using genetics is broadly done in three steps :

1. First, we find natural genetic variants located near the gene of interest. These variants are carefully chosen because they change the level or function of the protein we care about, without affecting nearby proteins.
2. Second, we test how these variants are linked to over 2,500 diseases and clinical biomarkers. This step can use different datasets than the first one, which helps increase the sample size to >1.5M individuals.
3. Third, we run statistical analyses to determine whether the protein is likely to have a causal effect on the disease.

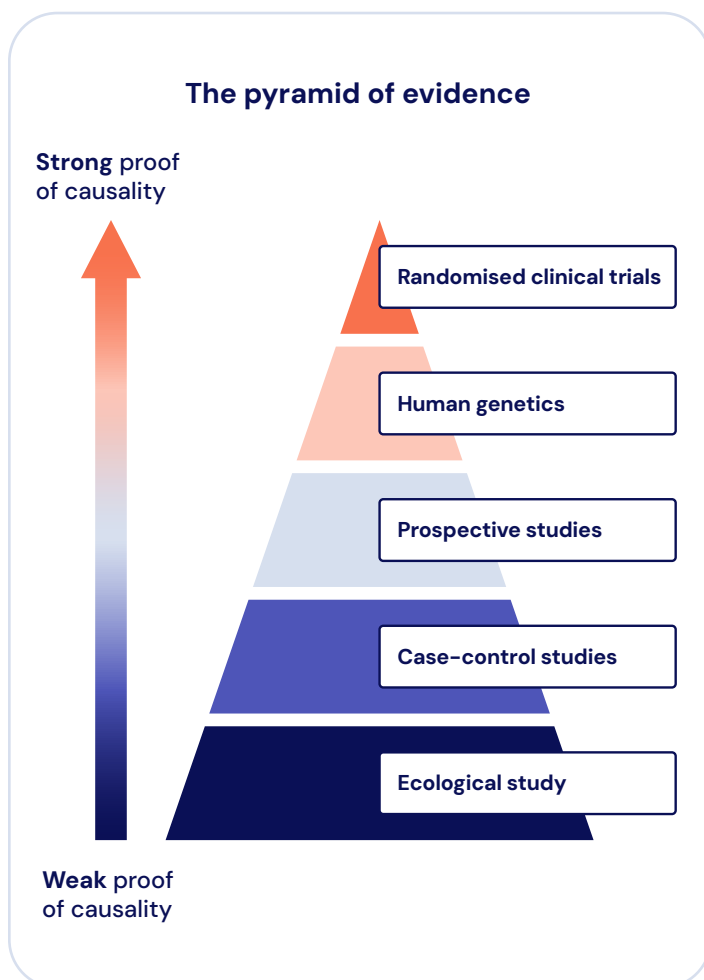


FIG 3. The pyramid of evidence. At the top of the pyramid: The gold standard to assess causality, the randomised control trial. At the bottom of the pyramid: traditional observational studies. These studies cannot discriminate whether the target causes the disease or whether the target is elevated as a result of the disease itself or unknown confounders. In between: Human genetics provides the highest level of causality in humans when randomised control trials are unfeasible.

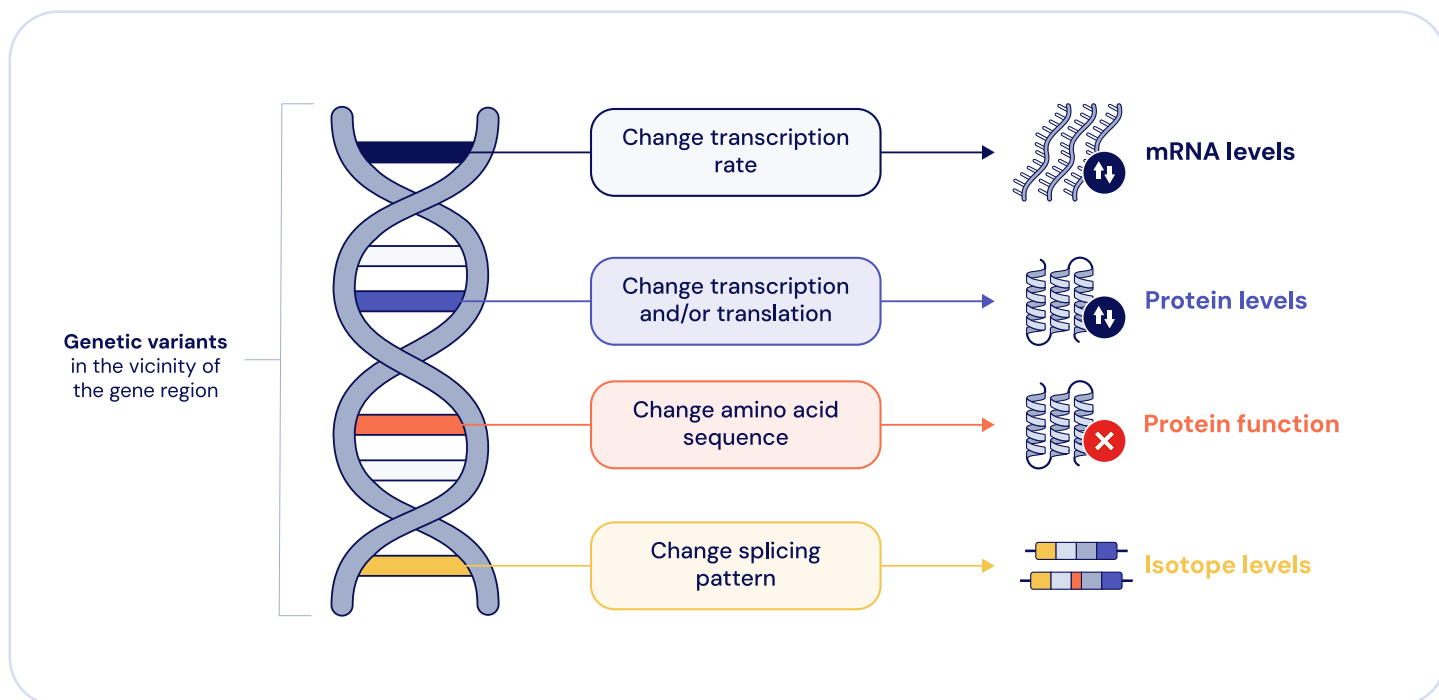


FIG 4. Genetic variants are carefully selected to infer causal effects of molecular targets on human diseases.

There is always a risk of choosing a target that won't work in patients, but this risk can be greatly mitigated by using human genetics. For example, if researchers had relied on human genetic data, they might have predicted that raising HDL cholesterol would not prevent cardiovascular disease. Genetic studies confirmed that higher HDL levels were not the causal factor and merely a correlate of heart disease risk. This insight could have redirected time and funding toward more promising programs. In many cases, failure is already built in when the target and indication are chosen. Human genetics can reveal this early and help avoid costly late-stage failures.

Human genetics can help you push your drug to the finish line by generating human evidence to inform your decisions and help you :

- Derisk your drug program and attract investments.
- Pinpoint the indications where your drug will achieve the highest clinical efficacy.
- Select biomarkers of efficacy for phase 1 dose escalation studies.

Our five steps plan to leverage Nature's randomized clinical trial :

1. You share your target and where additional insight could be most valuable.
2. We propose a tailored analysis plan for your consideration.
3. You approve it.
4. We generate genetic evidence to inform your program.
5. You move forward with greater confidence, backed by human data.

If you want to strengthen your drug discovery foundation, you can explore next steps with us here:

<https://calendly.com/eloigagnon-sparxgenomics/30min>

Or by sending us an email to ask your questions.
info@sparxgenomics.com

References

Dowden, Helen, and Jamie Munro. 2019. "Trends in Clinical Success Rates and Therapeutic Focus." *Nature Reviews Drug Discovery* 18 (7): 495–96. <https://doi.org/10.1038/d41573-019-00074-z>.

Minikel, Eric Vallabh, Jeffery L. Painter, Coco Chengliang Dong, and Matthew R. Nelson. 2024. "Refining the Impact of Genetic Evidence on Clinical Success." *Nature* 629 (8012): 624–29. <https://doi.org/10.1038/s41586-024-07316-0>.

Sun, Duxin, Wei Gao, Hongxiang Hu, and Simon Zhou. 2022. "Why 90% of Clinical Drug Development Fails and How to Improve It?" *Acta Pharmaceutica Sinica. B* 12 (7): 3049–62. <https://doi.org/10.1016/j.apsb.2022.02.002>.





sparxgenomics.com

