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Human genetics is becoming pharmacology's evidence base

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Whether human genetics supports the target is among the best-documented predictors of whether a new drug mechanism will reach approval. In 2015, across well-studied indications, the share of drug mechanisms with direct human genetic support rose from 2.0% at the preclinical stage to 8.2% among approved drugs, and selecting such targets was estimated to double the success rate of clinical development [1]. An independent analysis with updated pipeline data confirmed the effect, found it larger than two-fold when the causal gene is clear, and showed that for Mendelian associations it holds prospectively [2]. A 2024 analysis put the probability of success for mechanisms with genetic support at 2.6 times that of mechanisms without; the ratio varies among therapy areas and development phases and improves with confidence in the causal gene, but it is largely unaffected by the genetic effect size, the minor allele frequency or the year of discovery [3]. Pharmacology's evidence base for choosing a target is moving from animal models and pathway plausibility to the natural experiments recorded in human populations.

This is a pharmacological story as much as a genetic one. Human genetic variation approximates a natural experiment where the assumptions of the analysis hold: alleles are assigned at conception, an allelic series links partial and complete loss or gain of function to graded phenotypes, and Mendelian randomization reads out the consequence of lifelong exposure to more or less of a protein before any molecule exists to modulate it. What it returns is a direction of effect and a first safety signal, not a drug. The contrast with pharmacogenomics, which this journal reviewed in 2025, is one of subject: there the patient's genome chooses the drug and the dose, here the population's genome chooses the target [4]. The drugs approved against the products of *PCSK9*, *ANGPTL3* and *APOC3*, the latest of them in 2026, show that the second approach works on average; the lipoprotein(a) outcomes trial announced on 4 September 2026 shows that on average is not in every case.

The lipid clinic as proof of concept

PCSK9, which encodes proprotein convertase subtilisin/kexin type 9, entered pharmacology in 2003, when missense mutations in the gene were identified as a cause of autosomal dominant hypercholesterolemia, their gain-of-function mechanism established by later work. The therapeutic case was made three years later by the opposite alleles. In the Atherosclerosis Risk in Communities study, nonsense mutations in *PCSK9* carried by 2.6% of Black participants were associated with 28% lower mean low-density lipoprotein cholesterol (LDL-C) and an 88% lower risk of coronary heart disease (CHD), a hazard ratio of 0.11; a sequence variant carried by 3.2% of White participants, with 15% lower LDL-C, was associated with a 47% lower risk, a hazard ratio of 0.50 [5]. Moderate lifelong lowering had produced a large re-

duction in coronary events. Monoclonal antibodies against the PCSK9 protein were approved in 2015; in patients with atherosclerotic cardiovascular disease on statins, evolocumab lowered LDL-C by 59%, to a median of 30 mg/dL, and reduced the primary composite endpoint, with a hazard ratio of 0.85 and, over a median of 2.2 years, no significant difference in adverse events, including new-onset diabetes and neurocognitive events [6]. The same target has since been reached by three further modalities. Inclisiran, a small interfering RNA (siRNA), was approved in 2020–2021. Enlicitide, an oral macrocyclic peptide, lowered LDL-C by 55.8 percentage points against placebo at 24 weeks in 2,909 adults with, or at risk of, atherosclerotic cardiovascular disease [7] and was approved in the United States in July 2026 as the first oral PCSK9 inhibitor [8]. And in a phase 1 study, an adenine base editor designed to mimic the protective loss-of-function variants, delivered as messenger RNA and guide RNA in a lipid nanoparticle, inactivated *PCSK9* in the hepatocytes of 35 adults with heterozygous familial hypercholesterolemia (FH) or premature coronary artery disease after one intravenous infusion: reductions of PCSK9 of 51% to 88% and of LDL-C of 9% to 62% were dose-dependent and appeared durable through follow-up, which reached at least one year in 15 participants, with no dose-limiting toxicity [9]. One target, four modalities, twenty-three years, and the human variant as the constant.

ANGPTL3, which encodes angiopoietin-like 3, was defined as a target by a human knockout: exome sequencing of a family with familial combined hypolipidemia found compound heterozygous nonsense mutations, with low LDL-C, low high-density lipoprotein cholesterol (HDL-C) and low triglycerides together. In the DiscovEHR cohort, heterozygous loss-of-function carriers had lower triglycerides, HDL-C and LDL-C and 41% lower adjusted odds of coronary artery disease (odds ratio 0.59, 95% confidence interval [CI] 0.41–0.85); in the same report the monoclonal antibody evinacumab produced dose-dependent, placebo-adjusted reductions of fasting triglycerides of up to 76% and of LDL-C of up to 23% in humans [10]. Evinacumab was approved for homozygous FH in 2021.

APOC3, which encodes apolipoprotein C-III, completes the series. In the sequenced population, about 1 in 150 persons carried one of four rare *APOC3* mutations, three of them loss-of-function; carriers had 39% lower triglycerides, and in a subset of 13 carriers circulating apolipoprotein C-III was 46% lower; the odds of CHD among 498 carriers were 40% lower than among 110,472 non-carriers (odds ratio 0.60, 95% CI 0.47–0.75) [11]. Olezarsen, an antisense oligonucleotide (ASO) that suppresses the hepatic synthesis of apolipoprotein C-III, was tested in two phase 3 trials in 1,061 patients with severe hypertriglyceridemia randomized to 50 mg, 80 mg or placebo monthly: placebo-adjusted triglyceride reductions at 6 months of 49 to 72 percentage points across doses and trials, and an acute pancreatitis rate ratio of 0.15 (95% CI 0.05–0.40); liver-enzyme elevations and thrombocytopenia were more common at 80 mg, and the hepatic fat fraction rose with dose [12]. In the United States, olezarsen was approved for familial chylomicronemia syndrome in December 2024 and, in June 2026, to reduce triglycerides and the risk of acute pancreatitis in adults with severe hypertriglyceridemia; the siRNA plozasiran, against the same target, was approved there for familial chylomicronemia syndrome in 2025.

The pattern recurs across the three targets. In a 2023 survey that excluded oncology, 40 germline genetic observations had led to approved therapies for 4 common and 36 rare conditions; the median interval from genetic discovery to approval was 25 years, and the therapies for the common conditions were all inhibitors designed to mimic protective loss-of-function variants [13]. Genetics gave the direction and preliminary evidence on on-target tolerability, since carriers live with the variant lifelong; it did not establish the safety of stronger pharmacological suppression. The trials gave the magnitude; for the two newer targets the first indications were rare or severe diseases. The safety signal concerns the target, not the molecule: the thrombocytopenia seen with olezarsen at 80 mg is a question about the oligonucleotide and its dose, not about apolipoprotein C-III deficiency [12]. Approval, lipid lowering, pancreatitis prevention and prevention of coronary events are four different claims, and for the two newer targets the fourth has not yet been made.

What genetic evidence does not promise

The first limit is arithmetic: with about 10% of clinical programs reaching approval overall, a 2.6-fold relative advantage still leaves failure the likeliest outcome, and the probability for a particular program depends on its therapy area, its phase and the strength of the causal evidence [3].

The second is that genetics validates a target, not a trial. Dose, duration, timing and population belong to the trial, and the exposure they must approximate is lifelong. In a Mendelian randomization analysis of nine LDL-C-lowering polymorphisms in 312,321 participants, each 1 mmol/L (38.7 mg/dL) of lower LDL-C from early life was associated with a 54.5% lower risk of CHD, a threefold greater reduction per unit of LDL-C than the same difference achieved with a statin started later

in life [14]. A trial that lowers the same biomarker for a few years in patients who already have the disease tests a different exposure from the one the genome tested.

The third is the lesson of 4 September 2026: a causal hypothesis supported by genetic evidence does not by itself guarantee that a drug will reduce events. Two variants in *LPA*, the gene for apolipoprotein(a), that raise lipoprotein(a) (Lp(a)) carried odds ratios for coronary disease of 1.70 and 1.92, and the association of the two-variant genotype score with coronary disease was abolished after adjustment for the Lp(a) level, as mediation through Lp(a) predicts [15]. Mendelian randomization also gave the dose: the genetic association was proportional to the absolute change in Lp(a), 5.8% lower CHD risk per 10 mg/dL, so that an absolute reduction of about 100 mg/dL (101.5 mg/dL, 95% CI 71.0–137.0) would be needed to match the association of 1 mmol/L of lower LDL-C — a modeled equivalence, not a validated treatment threshold [16]. Pelacarsen, a hepatocyte-directed ASO, lowered Lp(a) by up to 80% against 6% with placebo in a phase 2 trial of 286 patients with cardiovascular disease [17]. The manufacturer then announced topline results of the phase 3 outcomes trial in 8,323 patients with established cardiovascular disease and Lp(a) of at least 70 mg/dL: the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and urgent coronary revascularization requiring hospitalization was not met against placebo, although Lp(a) was lowered, in a population receiving guideline-directed lipid-lowering and antihypertensive therapy; the full data are to be presented at a congress [18]. The announcement neither refutes the causal hypothesis nor shows that it needs no revision. What the trial did not demonstrate is the prespecified benefit under the conditions tested — this degree of lowering, for this duration, in this population, on this background; the effect estimates that would show which benefits it excludes have not been released. Several explanations are compatible with it, and none can be chosen before the data are presented: residual risk already well controlled by background therapy; years of treatment set against decades of exposure; the composition of the composite endpoint; and the genetic dose itself, since for a patient at the entry threshold of 70 mg/dL an 80% reduction is 56 mg/dL, about half the modeled equivalence, which predicts smaller benefits below that figure rather than none. Other Lp(a)-lowering agents remain in outcomes trials.

The fourth is that genetics also predicts failure, and can do so before a trial is run. A variant in *LIPG*, the endothelial lipase gene, raised HDL-C by 0.14 mmol/L, enough for epidemiology to predict a 13% lower risk of myocardial infarction; the observed odds ratio was 0.99, a 14-variant HDL-C score was likewise unassociated with myocardial infarction, and an LDL-C score built the same way was strongly associated [19]. Loss-of-function alleles in *PLA2G7* lowered lipoprotein-associated phospholipase A2 (Lp-PLA2) activity by 64%, the same as darapladib 160 mg (65%), and the causal risk ratios for CHD per 65% lower Lp-PLA2 activity ranged from 0.92 to 1.01 across the genetic instruments, with confidence intervals including one, against a pooled estimate of 0.95 for darapladib [20]. That analysis appeared online in December 2016 and in print in 2017, after darapladib had failed two phase 3 outcomes trials in 2014: a genetic comparison standardized to the activity decrement the drug itself achieves showed no coronary protection — evidence of a kind that can be assembled before a large outcomes trial rather than after it.

The fifth is that a validated target is not an arrived drug. Angiotensinogen has had human genetic support since 1992, when linkage and association between *AGT* and hypertension were reported, with higher plasma angiotensinogen for certain genotypes. Zilebesiran, an siRNA against hepatic angiotensinogen, lowered 24-hour ambulatory systolic blood pressure at 3 months by 14.1 to 16.7 mmHg against placebo after the initial subcutaneous dose, with lowering sustained to 6 months in the groups dosed every 6 months [21], and it is now in a cardiovascular outcomes trial with a planned enrollment of about 11,000 participants. The pharmacological novelty is the dosing interval, not the target.

The population base of this evidence is narrow. The cohorts behind it are mostly of European ancestry; every participant in the Lp(a) dose analysis was of white European ancestry [16]. None of the discovery studies cited here reports a Romanian cohort, and European ancestry in a discovery cohort is not Romanian representation in it. Effect sizes, and sometimes the variants themselves, do not transfer automatically from those cohorts to patients in a Romanian clinic.

What this asks of pharmacology

For those who read and run trials, the first question about a new mechanism is what the genetic support for the target is and how strong it is: a Mendelian disease, a coding variant with a measurable effect on the protein, or the phenotype of loss-of-function carriers, and whether those carriers show less of the disease the drug is meant to prevent. The second is whether the trial's dose and duration approximate the genetic exposure; a trial designed without that question tests a hypothesis the genome never tested.

For those who teach, Mendelian randomization and genetic target validation belong beside receptor theory and pharmacokinetics. A reader who can interpret a dose–response curve can interpret an allelic series, and the second skill now decides which drugs will exist for the first to describe.

For the journal, we invite work at the interface of human genetics and pharmacology: Mendelian randomization of candidate targets, the pharmacology of carriers of protective and deleterious variants, and studies in Romanian cohorts and carrier families, whose contribution to the discovery data only local work can build.

The 2.6 is a relative advantage, not a promise. The approvals of 2026 show what target selection from human genetics can deliver; 4 September 2026 shows that clinical benefit is established only in trials.

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