Connecting Biological Pathways with Clinical Outcomes: Developing Conceptual Models

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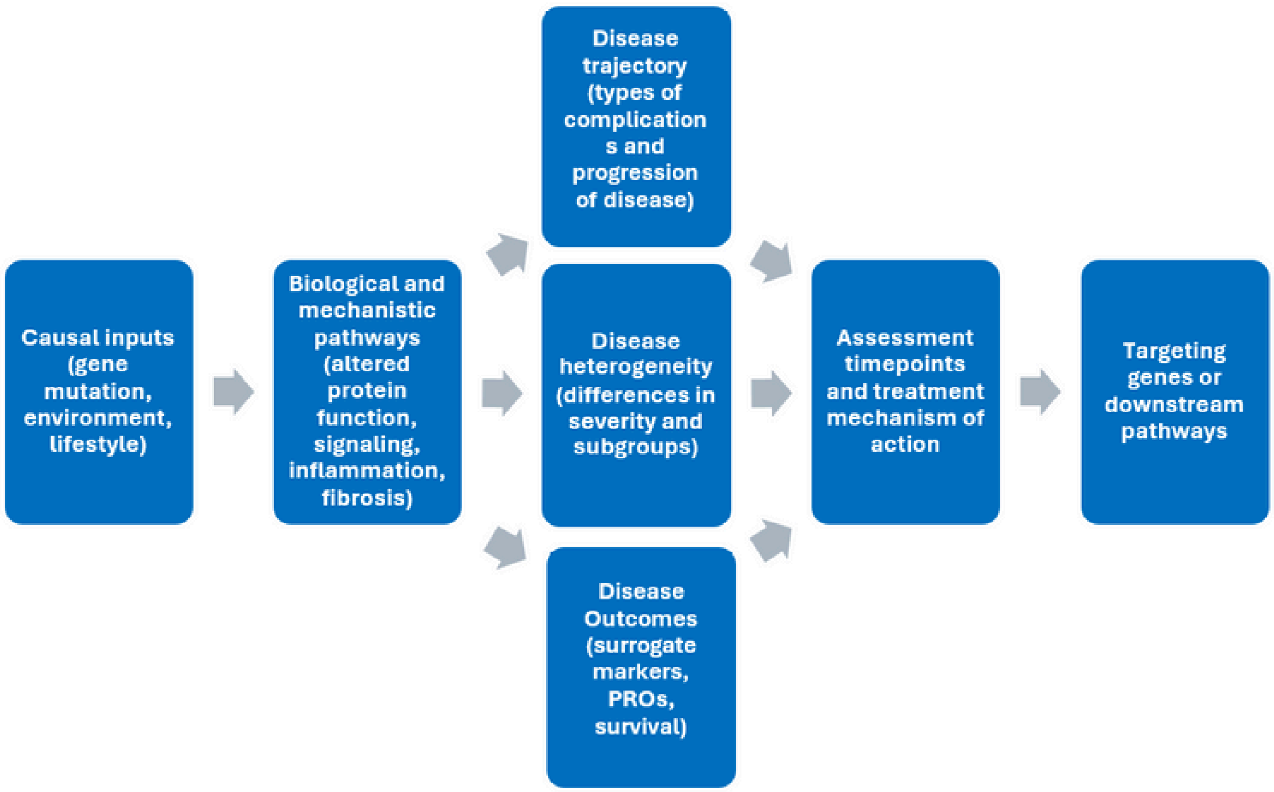
Healthcare teams and researchers often struggle to explain why patients with the same diagnosis and treatment can have very different outcomes. Conceptual models offer a structured way to make sense of this complexity by mapping how biological, psychological, social, and system-level factors interact to shape health.[1]

Conceptual models give regulators a map that connects mechanistic pathways to understand a disease or treatment effects, and helps develop and validate clinical endpoints.[2] The process of developing a conceptual model includes: laying the foundations (identifying resources for idea generation); selecting and structuring key factors (considering risk and protective factors); and making the model explicit and testable.

Figure 1: Theoretical example of a biological conceptual model



Different applications for developing a conceptual model include, but are not limited to[3-6]:

- To describe disease development
- To describe disease evolution
- To describe the biological process leading to a disease
- To describe the complex interactions between cofactors affecting the outcomes
- To describe how to evaluate a need for therapy (including which patients to select)
- To select new drugs for specific effects (for instance, the monoclonal antibodies to target one specific biomarker)
- To describe which Clinical Outcome Assessment (COA) to use to assess efficacy and at which time.

Within the FDA's patient-focused drug development (PFDD) framework, disease-level conceptual models are explicitly recommended as the foundation for selecting fit-for-purpose COAs and building endpoints that reflect the patient experience.[2] By outlining the patient journey throughout the disease, these models help reviewers understand which endpoints matter most to patients. Additionally, they guide where to position an intervention in the disease process and which mechanisms and biomarkers to emphasize.

In this blog post, we review primarily biological conceptual models and how they are connected to the understanding of disease and developing clinical outcomes.

Health conceptual models:

- Health conceptual models are structured representations, often diagrams plus explanatory text, that describe the key factors influencing different types of outcomes and the relationships between biological pathways, disease expression, and outcomes. They sit between abstract theory and empirical data, translating broad ideas into specific, testable pathways that can guide research, clinical decisions, economic modelling, and regulatory evidence packages **(Table 1)**.[1,3,4]

- A typical health conceptual model identifies predictors (for example, age, sex, socioeconomic status), intermediate processes (through the mechanistic pathways), and outcomes (for example, clinical markers, symptoms, and quality of life), and shows how these elements influence one another **(Figure 1)**.[1,4,7] By making assumptions explicit, conceptual models help teams align on what matters, the interventions to develop, and what data to collect across both trials and real-world evidence generation. The model represents a sophisticated hypothesis that requires validation; clearly articulating its underlying assumptions and expected outputs is essential for evaluating its validity.

Table 1: Conceptual models and other structured representations[3,4]

Term	Simple definition	When to use it
Conceptual model	Diagram of proposed causal linkages among a set of concepts related to a specific health problem or outcome.	To visually represent specific hypotheses, mechanisms, and risk/protective pathways you plan to test or target with an intervention.
Conceptual framework	Organized set of broad concepts or domains that provides an overall focus/rationale for integrating and interpreting information.	To map the categories/domains that might influence an outcome (for example, social–ecological layers) and scope what is possible to study or address.
Theory	Abstract set of interrelated concepts and propositions that explains and predicts phenomena across contexts.	To provide the underlying logic for why relationships in your conceptual model should exist and to guide question formulation and intervention content.
Logic model	Visual map linking program resources, activities, and outputs to short-, medium-, and long-term outcomes.	To describe how a specific program is supposed to work in practice and to plan or evaluate implementation.
Directed acyclic graph (DAG)	Graph of variables connected by one-way arrows representing assumed causal relations, with no closed loops.	To clarify which variables are predictors, confounders, mediators, and outcomes in statistical analyses and to inform adjustment strategies.

Core building blocks

Drawing on public health and health informatics guidance, a practical, cross-disciplinary process for developing a conceptual model has three main phases.[3,4]

1. **Lay the foundations (identify resources that support idea generation)**
    - Start by scanning existing theories, frameworks, and models in your topic area, alongside input from clinicians, methodologists, patients, and policy stakeholders.
    - Be explicit about which disciplinary perspectives (for example, epidemiology, behavioral science, informatics, systems science) you are integrating and where current models fall short.

2. **Select and structure key factors (consider risk and protective factors)**
    - Identify risk and protective factors across levels (individual, interpersonal, organizational, community, structural) and over time, then prioritize those most relevant, evidence-supported, and measurable for your question.
    - Define each construct clearly and specify the hypothesized relationships (for example, causal, mediating, moderating, feedback loops) between them.

3. **Make the model explicit and testable (select factors for inclusion in the model)**
    - Develop a clear narrative description plus a visual diagram that together explain the logic of the model.
    - Seek feedback from diverse stakeholders to refine content and structure, then use the model to derive specific research questions, intervention targets, and indicators for data collection and evaluation.
    - Treat the model as iterative, updating it as new evidence and contextual changes emerge and sharing it publicly so others can critique and build on it.

Regulatory perspective

Regulators also rely on conceptual models, particularly in patient-focused drug development and clinical outcome assessment.[8] FDA's Patient-Focused Drug Development guidance series describes disease-level conceptual models that organize how signs, symptoms, functional impacts, and health-related quality of life relate to one another and to potential trial endpoints.[9] These models are developed using literature, clinical expertise, and qualitative patient input, and then used to justify which COAs and endpoints are most relevant and meaningful in a given indication.[9]

An example includes how, in treatment-resistant depression, Katz et al. (2022) used esketamine to show how systematically planned patient-experience data can strengthen a New Drug Application (NDA) without replacing traditional endpoints.[2] The authors developed the conceptual framework for esketamine through a systematic process starting with Phase 2 clinical trials, where they conducted qualitative patient interviews and literature reviews to identify key patient-relevant concepts in treatment-resistant depression. As a result, core domains including symptom severity (e.g., depressive symptoms aligned to DSM-5 criteria), functional disability (social, family, work impacts), comorbid anxiety, and treatment burden were captured. From the framework, the phase 3 TRANSFORM and SUSTAIN trials incorporated validated PROs as key secondary and secondary endpoints. A patient-preference study during drug development quantified how patients trade off the magnitude and speed of depression relief against esketamine's risks and burdens, which outlined the benefit–risk of the intervention. These PRO and preference data were integrated across the NDA, FDA advisory committee briefing materials, and the sponsor's benefit–risk modelling. FDA's clinical review explicitly acknowledged that functional and preference results were reviewed and considered supportive of the primary efficacy findings and of patients' acceptance of the benefit–risk profile.

EMA documents on COA implementation similarly describe using patient and expert input to validate the conceptual model for a disease and to identify patient-relevant concepts that should be captured in endpoints.[10] The FDA Patient Reported Outcomes Guidance and PFDD Guidance documents serve as roadmaps for EMA and global regulatory bodies. In health economics, conceptual modelling is recognized as the process of specifying the structure, variables, and causal relationships that will later be implemented as a decision-analytic model, with the quantitative model understood as a subset of the broader conceptual representation.[7]

Biological example: pathogenesis model of type 1 diabetes

Atkinson et al. (2015) present an evolving biological conceptual model of type 1 diabetes that moves beyond the classic linear model toward a heterogeneous, multi-component disease system for understanding drug development.[11] Historically, type 1 diabetes was viewed as a T cell–mediated autoimmune condition in which an environmental trigger initiates progressive β-cell destruction, culminating in near-complete β-cell loss at diagnosis. More recent organ donor, imaging, and clinical data challenge this view, highlighting marked inter-individual variability in β-cell mass, evidence of residual β-cells and C-peptide years after diagnosis, and a broader inflammatory process that also involves exocrine pancreas tissue and potential viral persistence.

In this biological model, disease development arises from interactions between several components: immune responses, β-cell function, pancreatic tissue, environment, and genetics.[11] These elements collectively shape the rate and pattern of β-cell loss, which appears non-linear, relapsing–remitting, and age-dependent, rather than a single linear decline. Importantly, the authors link this updated model directly to how interventions are viewed. Trials often built on singular assumptions (for example, near-complete β-cell loss at diagnosis, continuous immune attack, or homogeneous disease) tended to use short-term, single-target immunotherapies and often failed. In contrast, the emerging systems support longer-term, combination strategies that target both immune pathways and β-cell survival or proliferation.

Over time, the model has been refined by incorporating multiple features such as innate immune activation, chronic exocrine inflammation, small pancreatic size, variable baseline β-cell mass, and environmental modifiers like the microbiome and diet **(Table 2)**.[11] Together, these refinements create a conceptual model that better accounts for observed heterogeneity in age at onset, progression rates, response to therapy, and long-term residual function.

Table 2: Components seen in biological conceptual models of type 1 diabetes

Component	What it covers
Immune processes	Central and peripheral tolerance defects; autoreactive CD8 and CD20 cells; innate antiviral signalling
β-cell function	Baseline β-cell mass variability; vulnerability to inflammatory and metabolic stress; residual β-cells and C-peptide in long-standing disease.
Pancreatic tissue	Small pancreas phenotype; exocrine inflammation and infiltrates; subclinical pancreatitis.
Environment & genetics	Microbiome; diet; infections; antibiotic use; exercise; epigenetic influences; susceptibility genes.
Disease trajectory & outcomes	Non-linear, episodic β-cell loss; age-dependent subtypes; persistent β-cell function in many adults; mismatch between biomarkers and true β-cell mass.

Using and developing conceptual models well

Good conceptual models are explicit, evidence-informed, and transparent about their assumptions and limitations. When applying an existing model, it is important to assess whether its constructs and relationships fit the target population, healthcare context, and decision problem, especially because many models are developed in specific countries or systems. By integrating mechanistic–biomarker–outcome pathways with contextual factors, conceptual models can bridge basic science, clinical trials, real-world practice, and regulatory decision-making, providing a shared map for improving patient outcomes.

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