

WHITE PAPER

What Does It Take to Make Progress in a Disease?

June 2023

By Michael S. Ringel, Julie Dethier, Michelle J. Davitt, Maria Denslow, R. Andrew Fowler, Sebastian C. Hasenfuss, and Ulrik Schulze

What Does It Take to Make Progress in a Disease?

Abstract

In this paper, we investigate what conditions need to be in place to make progress in combating a disease using a case-control design: we compare cases (diseases with a successful therapy) to controls (diseases without a successful therapy). We find five conditions (“hurdles”) must typically be cleared for success: (A) understanding of biological drivers, (B) ability to modulate biology, (C) availability of translational models, (D1) ability to identify patients, and (D2) ability to measure clinical response. This framework is similar to ones deployed to evaluate individual drug candidates but is employed here to make inferences about entire diseases. It can be used to identify diseases most ready for progress, where efforts should be focused to make progress in diseases that are currently intractable, and where the industry could benefit from development of tools to address the hurdle that is most commonly the last to be cleared across diseases—namely, (C) translational models.

Introduction

Biopharmaceutical research and development (R&D) is a difficult, lengthy, expensive, and risky process.^{1,2,3,4,5,6} In particular, despite a recent resurgence in R&D success rates,^{7,8,9} the vast majority of R&D projects ultimately fail, resulting in lost opportunity to bring new medicines to patients and wasted expense and effort.^{10,11,12,13,14} The most effective single lever for improving R&D productivity is to reduce this cost of failure, either by increasing overall success rates or by shifting failures earlier, thus freeing up capacity to be deployed to other, higher-probability projects.^{6,15,16}

A number of biopharmaceutical companies have explored ways to improve their decision-making regarding which R&D projects to continue and which to terminate, by increasing the quality of information available to decision-makers, the quality of the decision-making process itself, or both.^{17,18,19} In particular, a number of companies have laudably introduced asset-level frameworks that require validation that scientists are pursuing the “right biological target” to have an effect on the disease, using the “right molecule” to engage the target both effectively and safely, testing the hypothesis in the “right patients” to see an effect, and so on.^{20,21,22} It is plausible that these efforts, coupled with a significant increase in known disease targets with human validation via “omics tools,”^{23,24,25} are behind the recent improvements in R&D success rates and cost of failure.⁷

This framework regarding predictors of success probability has generally been applied at the level of individual drug candidates. In this paper, we argue that the framework also works well at a level above drug candidates: entire diseases. That is, one can predict whether success in fighting a disease is likely by applying this framework. We provide evidence for this assertion by conducting a “case-control” study of “cases” (diseases for which a successful therapy has been developed) versus “controls” (diseases without a successful therapy) and the association between these states and the status of five predictor variables (“hurdles” to overcome, described in more detail ahead). Moreover, not only does this framework provide a lens into whether progress in combating a disease is likely, but it also provides a guide as to which hurdles should be the focus of attention in order to address a currently intractable disease. Lastly, by examining which hurdles show up most frequently as barriers to progress across multiple diseases, this framework provides a guide for industry and academia on what efforts might be helpful to improve the chances of success more broadly across all diseases—the missing link in drug R&D.

Framework

The events necessary to discover and develop a drug are typically divided into a step-wise sequence starting with discovery biology followed by lead generation and optimization, preclinical testing, and ultimately clinical validation and submission to regulators (see Exhibit 1). There is no absolute reason the activities of drug R&D need to be linear or follow exactly this order, and indeed there are many instances in which it has not followed the archetypal sequence. For example, many drug development efforts in oncology and rare disease have employed a hybrid approach that goes straight from Phase I safety testing in patients to Phase III trials.^{26,27} Furthermore, the history of drug R&D is replete with examples of phenotypic discovery for which targets were never identified,^{28,29,30,31,32} or for which the sequence of activities happened in virtually every permutation of the archetype.³³ Lastly, the exact tools used today need not remain the tools used going forward: for instance, while preclinical evidence generation has historically relied on animal models and biochemical assays, these have proven to be poor predictors of human-organism-level responses.^{34,35,36} As a result, there is an emerging potential to augment or replace these tools with human genetic evidence^{23,25} and organoid, organ-on-a-chip, or in-silico methods.^{36,37,38,39,40,41,42}

This being said, at a conceptual level, there are still four key questions that must be answered, in whatever sequence and manner, to develop a new therapy, with the caveats mentioned previously. These questions are: i) Is there an aspect of biology available that can affect disease pathophysiology? ii) How can that biology be modulated? iii) What evidence is sufficient to allow testing this hypothesis in humans? and iv) What evidence is sufficient to enable a regulator to approve clinical use in patients? Based on this, we hypothesized that there are five hurdles that generally need to be cleared for success in a disease area (as illustrated in Exhibit 1): (A) understanding of biological drivers, (B) ability to modulate biology, (C) availability of translational models, (D1) ability to identify patients, and (D2) ability to measure clinical response—with the final two hurdles being related aspects of successful clinical development.

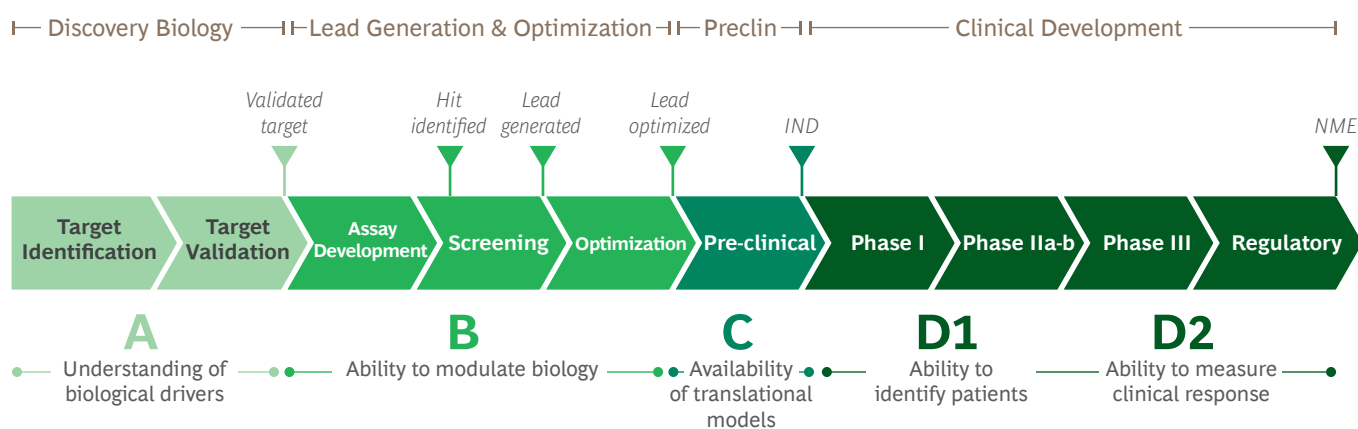


Exhibit 1: Steps in drug R&D with the five hurdles highlighted. This archetypal sequence of activities covers four main steps: discovery biology to elucidate and validate biological drivers of interest, lead generation and optimization to determine how to modulate the biology of interest, preclinical testing of safety and efficacy, and clinical testing in humans, typically in a stepwise fashion covering Phase I, safety testing in normal, healthy volunteers, Phase IIa dose determination, Phase IIb clinical proof-of-concept, and Phase III registrational studies. Each of these four steps corresponds to the five hurdles to clear for success in a disease area, with clinical testing in humans having two hurdles: ability to identify patients and measure clinical response. IND = investigational new drug filing, NME = new molecular entity approval by regulatory authorities.

Methods

We compared “cases” (diseases that have a successful therapy) against “controls” (diseases that do not have a successful therapy) across disease areas to identify patterns common to diseases with successful therapies versus without. We used 16 disease areas as defined by Anatomical Therapeutic Chemical (ATC) classification codes, and selected two high-prevalence cases and two high-prevalence controls within each disease area for a total of 64 diseases analyzed. We excluded diseases that were not defined clearly enough, clinical presentations of many disease types, descriptions of procedures, and conditions caused by malnutrition or poisoning (see exhibit 2). We defined success as the existence of an approved drug therapy with significant impact on clinical outcomes. We restricted our analysis to the time period prior to the COVID-19 pandemic to avoid potential transient effects (e.g., disruption of clinical trials) that are not expected to persist post-pandemic.

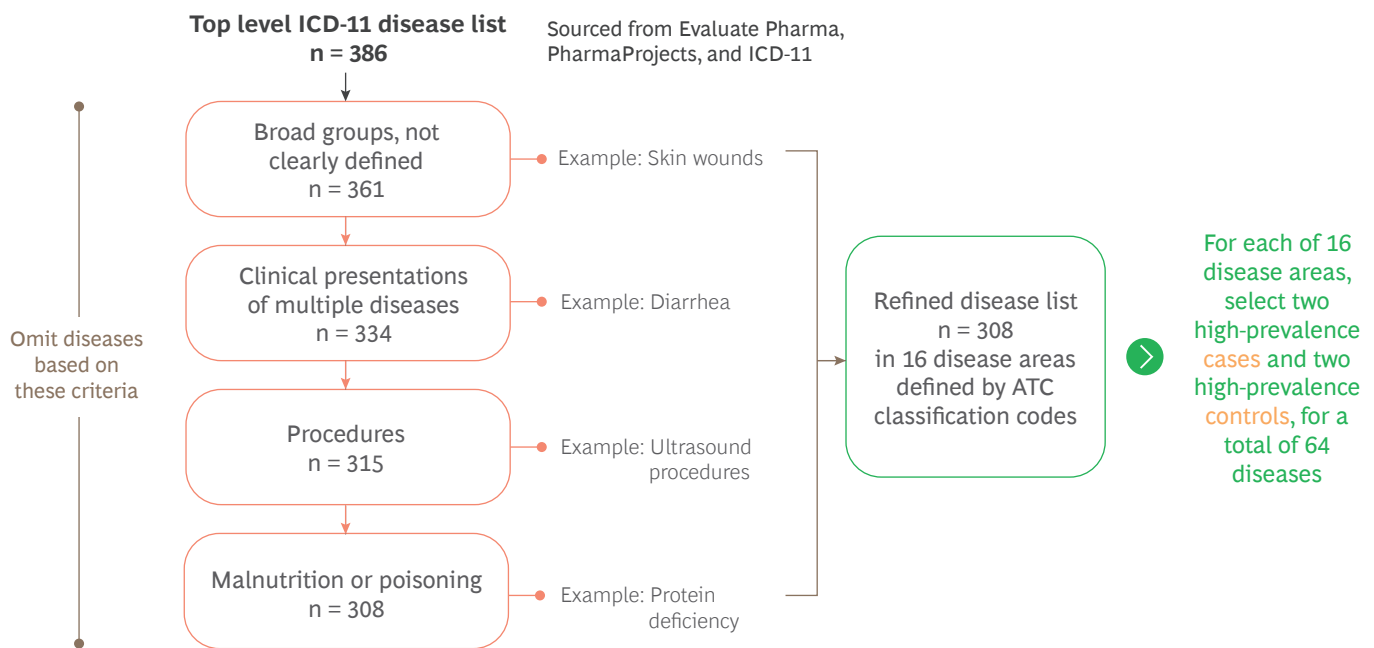


Exhibit 2: Selection scheme for included diseases. The cases and controls for the analysis were obtained by selecting two cases and two controls each with high prevalence in the US from each of 16 disease areas, filtering diseases that fit one or more of the criteria in the exhibit. ICD-11: international classification of disease, revision 11. ATC: anatomical therapeutic chemical.

For the selected diseases, we then scored achievement against each of the five hurdles, scoring two ways: First, we asked a set of 18 physicians each independently and blindly (i.e., agnostic of the hypothesis being tested) to score each disease. Second, we performed our own literature analysis to score the diseases, in particular paying attention to the clearance of the hurdles prior to the launch of therapy, and found similar results to the physician-driven approach.

Each of the five hurdles was scored using a rubric that defined a four-point scale (0 to 3), with one point awarded for each of three elements that could be true for each hurdle, as described below.

For hurdle (A), understanding of biological drivers, the elements were the following:

- Disease driver has been identified (genetically or otherwise).
- Strong gene-disease association exists (clinical and supporting experimental evidence provided by multiple studies).
- Many single-nucleotide polymorphisms are associated with the gene-disease pair, or there is a well-known mechanism of action for non-genetic drivers.

For hurdle (B), ability to modulate biology, the elements were the following:

- Target class is accessible (e.g., experience in target class, or known manner of access).
- Target class has been successfully targeted in the past.
- Organ/cell type easily accessible (e.g., does not need to cross the blood-brain barrier).

For hurdle (C), availability of translational models, the elements were the following:

- Models have same driver (gene/mutation or other) as in human disease.
- Models have similar in vivo context to human disease (e.g., chronic vs. acute, immunosuppressed, specific diet).
- Models display a phenotype similar to that of human disease.

For hurdle (D1), ability to identify patients, the elements were the following:

- A diagnostic exists that is specific and sensitive.
- The diagnostic is minimally invasive, safe, inexpensive, and easy to perform (e.g., blood/urine test, physical exam, questionnaire, ultrasound or x-rays versus biopsy, endoscopy, CT scan, or MRI).
- Robust biomarker(s) allows patient stratification.

For hurdle (D2), ability to measure clinical response, the elements were the following:

- A test exists that is specific and sensitive.
- The test is minimally-invasive, safe, inexpensive, and easy to perform (e.g., blood/urine test, physical exam, questionnaire, ultrasound or x-rays versus biopsy, endoscopy, CT scan, or MRI).
- The test allows real-time updates and a dynamic view of patient state.

Each hurdle was considered cleared for a disease if the score was greater than or equal to 2 points (i.e., at least two elements were true). For hurdle (B), ability to modulate biology, no score was assigned if the target was not known. Timing of hurdle clearance was determined based on a literature review and timing of a therapy on the approval or marketing start date for the drug, and in our literature review-based scoring, we only included clearance of a hurdle if it preceded the achievement of the therapy approval or marketing start date. To estimate the venture capital (VC) investment against each hurdle, we grouped companies with VC funding into nine categories: Target, Modality, Platform, Model, Diagnostic, Device, Drug delivery, Computational/Digital, and R&D model. We then computed the proportion of companies in each category.

Results

Clearing the hurdles independently and collectively correlates with progress in a disease.

In comparing cases versus controls, we find that clearance of the hurdles does correlate with progress in developing therapies for diseases. In one-way ANOVA comparisons, each of the hurdles shows a statistically significant correlation with the development of the therapy, except for hurdle (A), understanding of biological drivers. Furthermore, the five-way interaction term for achievement of all hurdles is also significant, indicating that success is most likely achieved when all hurdles are cleared (see table 1). Using a random forest model, we find strong predictive power with an area under the receiver operating characteristic curve of 0.91; that is, for a false positive rate of 11%, 85% of true positives were identified in the test set.^{43,44}

Hurdle	Significance (p value)
(A) understanding of biological drivers	0.316 (not significant)
(B) ability to modulate biology	0.009
(C) availability of translational models	0.024
(D1) ability to identify patients	0.009
(D2) ability to measure clinical response	0.036
Interaction: no hurdle failed	0.000

Table 1. Results of one-way ANOVA. In one-way tests of the correlation of progress in combating a disease with each of the variables independently as well as an interaction term that is true only if no hurdle has failed to be cleared, each of the correlations is significant except hurdle (A)—see text for full explanation.

Hurdle (A), understanding of biological drivers, was not significant in our analysis. This is not entirely surprising given the many times phenotypic drug development without target understanding has been successful.^{28,29,30,31,32,33} However, there is a trend toward greater understanding of biology in cases versus controls (see exhibit 3), which we interpret as clearing hurdle (A) being not an absolute condition precedent but still valuable in many situations; that is, there is merit in both target-based and phenotypic screening approaches. We see evidence for this in the fact that the interaction effect across all hurdles is significant. We suspect that, with a larger sample size, we would be able to discriminate a direct signal for hurdle (A).

Hurdle (B), ability to modulate biology, does correlate with success; however, it is increasingly rare to find situations in which the biology is inaccessible to modulation. Over the last several decades, there has been a profusion of new modalities able to access virtually all target space,^{45,46} as well as advances in approaches for traditional modalities such as structure-based drug design (SBDD) that have improved the ability of these modalities to modulate previously intractable targets.^{47,48,49} Although out of scope for this analysis, the response to the COVID-19 pandemic is an instructive example, with both new modalities such as mRNA^{50,51} and viral vectors,^{52,53} by-now-established modalities such as monoclonal antibodies,^{54,55,56,57,58} and more-established modalities such as protein subunits⁵⁹ and small molecules^{60,61,62,63} (some enabled by SBDD⁶⁴) all playing a role. This expansion of our therapeutic armamentarium has led to novel therapies for a variety of diseases, including many cancers and autoimmune disorders such as multiple sclerosis, asthma, and rheumatoid arthritis.^{65,66,67,68,69}

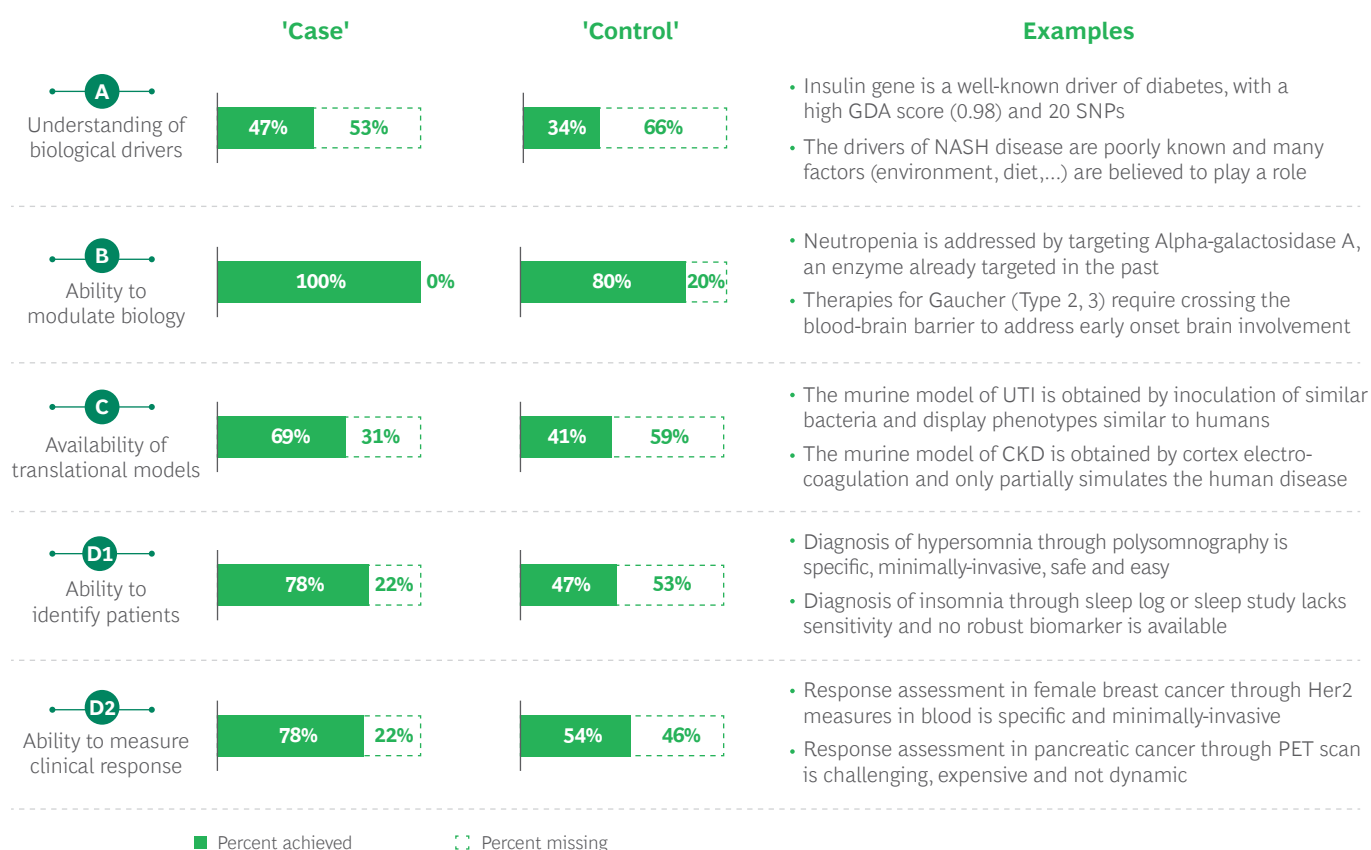


Exhibit 3. Correlations of hurdles with development of successful therapy. Each of the hurdles is more frequently cleared for cases versus controls (though not statistically significant for hurdle (A)). GDA: gene-disease association, NASH: non-alcoholic steatohepatitis, UTI: urinary tract infection, CKD: chronic kidney disease, PET: positron emission tomography.

Hurdle (C), availability of translational models, has a low level of achievement for both cases (69%) and controls (41%). Critically, however, it is most often the last hurdle to be cleared—true in 50% of all cases (see exhibit 4). The availability of a good translational model has often been the factor unleashing the ability to innovate (a topic to which we return in the Discussion section).

Lastly, hurdles (D1) ability to identify patients and (D2) ability to measure clinical response are the hurdles with the largest difference between cases and controls, true in nearly 80% of cases but only 47% and 54% of controls, respectively.

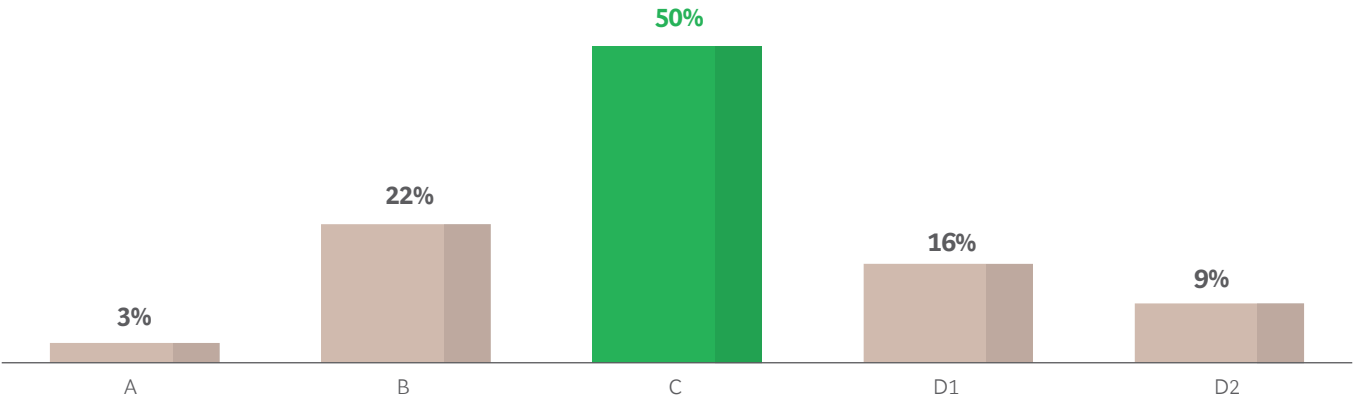


Exhibit 4. “Last hurdle to be cleared” among cases. For cases (diseases with successful treatment), the last hurdle to be cleared (when including only hurdles cleared pre-approval) is most frequently hurdle (C), availability of translational models.

Discussion

Inferences about diseases ready for progress

Our model allows for predictive analysis. At the time we conducted the analysis, there were several diseases in our control set with four of the five hurdles cleared. We would predict that these diseases are more ripe for progress. Indeed, this has since proven to be the case for one of the diseases in our control set: Duchenne Muscular Dystrophy (DMD). The genetic driver of the disease was well-known: mutations in the DMD gene alter the structure or function of dystrophin or prevent any functional dystrophin from being produced.^{70,71,72} Available translational models (e.g., the X chromosome-linked muscular dystrophy (mdx) mouse)⁷³ provided a valuable model for DMD in humans, albeit with a milder muscle-wasting phenotype than in humans.⁷¹ Diagnosis for DMD was specific and sensitive thanks to genetic testing and muscle biopsy. In addition, plasma creatine kinase level, which is expressed in muscle and brain cells, offered a robust biomarker for the disease.^{71,72} Yet, at the time of the analysis, limited therapeutic options were available for treatment of DMD,^{70,71} with glucocorticoids the mainstay of treatment. Sarepta's Exondys 51 (eteplirsen), based on exon-skipping technology, was conditionally approved by the U.S. Food and Drug Administration (FDA) in 2016 for DMD patients with mutations in the dystrophin gene amenable to exon 51 skipping.⁷⁴ Yet, in 2018, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a negative opinion of eteplirsen for the treatment of DMD.⁷⁵ But since 2019, three more therapies for DMD have been approved by the FDA: Sarepta's Vyondys 53 (golodirsen) for exon 53 skipping in December 2019,⁷⁶ Nippon Shinyaku's Vilepso (viltolarsen) for exon 53 skipping in August 2020 (also approved in Japan),⁷⁷ and Sarepta's Amondys 45 (casimersen) for exon 45 skipping in February 2021.⁷⁸

Taking a snapshot at the present time, we can see other diseases that have currently cleared four or five of the hurdles but do not currently have an approved therapy with a significant clinical benefit. An example is hereditary angioedema (HAE). The genetic drivers of the disease are well-known: mutations of the C1NH/SERPING1 gene encoding the C1 inhibitor (C1INH) lead to plasma deficiency and recurrent attacks of severe swelling.⁷⁹ There are murine models that share the same disease etiology (disruption of the C1INH gene)⁸⁰ and the same clinical features (acute hereditary angioedema attacks).⁸¹ Patients can be identified by specific and sensitive laboratory tests (biomarker measurement of serum antigenic C4) confirmed by screening for the SERPING1 or C1NH genes.^{82,83} Yet, therapeutic options are currently limited, focused on symptom management and not long-term prophylaxis (LTP).^{84,85} New drugs are being investigated for LTP. Some, such as KalVista's sebetralstat, exert an anti-plasma K action to inhibit the kallikrein-kinin system.⁸⁶ Others, such as Ionis's donidalorsen, act by inhibiting prekallikrein, with a subsequent decrease in plasma K.⁸⁷ Still others, such as CSL's garadacimab, block factor XII.⁸⁸ Our framework suggests that at least one of these therapies should prove successful.

Actions to make progress in a currently intractable disease

Contrary to the situation with DMD and HAE, there are many diseases for which a number of the conditions for progress are currently missing. This is not a call to eschew R&D in these areas; instead, it can be a roadmap for the actions most necessary to make progress by focusing attention on the key gaps. Per the analysis in [exhibit 4](#), often the key gaps to be resolved are (C) availability of translational models and (D1) ability to identify patients with suitable biomarkers, as well as (perhaps more historically, given many recent advances in modalities) (B) ability to modulate biology. One pertinent example is nonalcoholic steatohepatitis (NASH). Experts are not sure why some people with non-alcoholic fatty liver disease have NASH while others have simple fatty liver.^{89,90} Available models, although providing critical guidance in understanding specific stages of the disease pathogenesis and progression, require further development to better mimic the disease spectrum in order to provide both increased mechanistic understanding and identification/testing of novel therapeutic approaches.^{91,92,93} Specific diagnosis is challenging and liver biopsy remains the gold standard for definitive diagnosis.^{94,95}

Patterns across diseases

The last kind of inference that can be made from our findings is one regarding patterns across diseases. Are there certain keys to success that can be gleaned from our analysis that might point to untapped areas of opportunity?

We found in the analysis that the last hurdle to fall is typically hurdle (C), happening as frequently as all the other hurdles combined. An illustrative example is the history of developing a cure for hepatitis C. Hepatitis, or inflammation of the liver, has long been a part of human history. The symptoms can be severe, including abdominal pain, tiredness, jaundice (the yellowing of skin and eyes), and even liver failure and death.⁹⁶ Patients with hepatitis C could be identified reliably from 1989^{97,98} and their responses measured quantitatively from 1993⁹⁹ when diagnostics were developed that honed in on what was then known as non-A non-B hepatitis. Viral targets were known and accessible to small molecules from 1993,¹⁰⁰ and yet, despite repeated efforts by companies such as Roche and Chiron, development proved fruitless. Unlike in many other infectious diseases, it was not possible to grow the pathogen in culture, leaving one key hurdle still in place. The wasted effort to cure hepatitis C before all the hurdles were overcome contributed to the poor performance and ultimate demise of Chiron Corporation as an independent entity—and of course left patients with a large, unmet need.^{101,102} The discovery of the replicon model in 1999¹⁰³ proved to be the unlock, with—just a few years later, in 2003—Pharmasset running the screens that led to teleprevir,¹⁰⁴ ushering in the era of direct-acting antivirals that specifically target hepatitis C. Today, cure rates for chronic hepatitis C are 90%—an incredible outcome for a previously chronic and sometimes fatal disease.¹⁰⁵

The hepatitis C story is not unique and in fact is the most common pattern. According to our analysis, lack of good preclinical models remains the key stumbling block across diseases, with many models based on animals or biochemical assays having low correlation to the human organism.^{106,107,108} In particular, the models for chronic and progressive diseases, which represent the bulk of disease burden,¹⁰⁹ often fail to recapitulate the slow, degenerative nature of these diseases.^{107,108} This has been particularly challenging in neuroscience, where animal models have even less correlation given the uniqueness of human brain expansion during development,³⁷ and least challenging in infectious diseases where often only the pathogen needs to be modeled.¹⁵ This disparity has resulted in neuroscience typically having the lowest success rates in development, and infectious disease the highest.¹⁵

An emerging response from biopharmaceutical leaders when faced with this problem is to minimize the reliance on animal and assay-based models and focus more on what we can learn from human genetics:^{23,24,25} omics datasets properly coupled to longitudinal phenotypic data can reveal much about what can be important in disease,^{110,111} and when followed up with functional assessment of targets, can be a powerful way to identify and validate targets.^{112,113} This is indeed an appropriate response—one that has been responsible for recent improvements in productivity,^{7,25} and which, according to the findings in our current study, should very much be a focus of even deeper efforts going forward. It is a particularly appropriate approach for monogenic diseases, which should not be underestimated, as there are now more than 4,000 such identified conditions.¹¹⁴ However, it can be challenging for many other diseases, given the high polygenicity of many conditions and pleiotropy of the genes involved.¹¹⁵

Solving this issue—finding preclinical models that accurately predict human clinical response—is more important than is typically given credit by the industry.^{39,116} Even small changes in predictive value in preclinical can have large impacts on the total productivity, perhaps as much as increasing pipelines tenfold.^{117,118} So it behooves the biopharmaceutical industry and those that support it to make progress on this element of the drug development value chain that is so critical and yet currently so underdeveloped.

The missing homunculus

In medieval literature, a homunculus was a miniature human created in a flask by alchemy.¹¹⁹ Imagine a perfect homunculus that fulfilled the following criteria: exact recapitulation of human clinical response, faster than real time, inexpensive, easy to use, and fully ethical to employ for drug testing. What would drug developers do differently? They would test much more rapidly and iteratively. Successes in the lab would guarantee successes in the clinic, and even failures would rapidly advance our understanding and contribute to better overall future success rates.

No preclinical system with the features of a perfect homunculus exists today, but its absence cannot yet be attributed to impossibility, given the relatively little effort that has been deployed to create one (see ahead). There are a range of possible avenues to explore to develop, if not a true homunculus, at least preclinical tests with much greater predictive value. These include organoid,^{37,40,120,121,122} organ-on-chip, body-on-chip,^{123,124,125,126} cell culture,^{38,41,127,128} explant,¹²⁹ human phase zero,¹¹⁶ and in silico^{130,131,132} solutions. It is beyond the range of this paper to delve specifically into each of these or determine which might be most fruitful. Whatever is selected, there should be rigorous backtesting of both clinical failures and successes to determine the predictive value of the system(s).¹³³

A corollary to creation and validation of models with predictive value is elimination of models with low predictive value. Too often, there is a dearth of backtesting such that it is unknown whether the models in current use are actually predictive. The predictions made by the models are not always even heeded, and yet they remain in use for no clear reason other than legacy, with positive results lauded, but negative results explained away.^{134,135,136,137}

Despite the importance of better translational models, there is very limited activity to develop them. Academic labs have made initial forays, but have not typically developed models to full fruition. Pharmaceutical companies have much of their budgets deployed in asset-specific activities, and have not undertaken efforts of significant size to develop and back validate cross-program preclinical models. VC companies have made only extremely limited investments. Our own analysis finds that almost all VC investment is concentrated on hurdles (A) and (B), with less than 1% on hurdle (C) (see Exhibit 5).

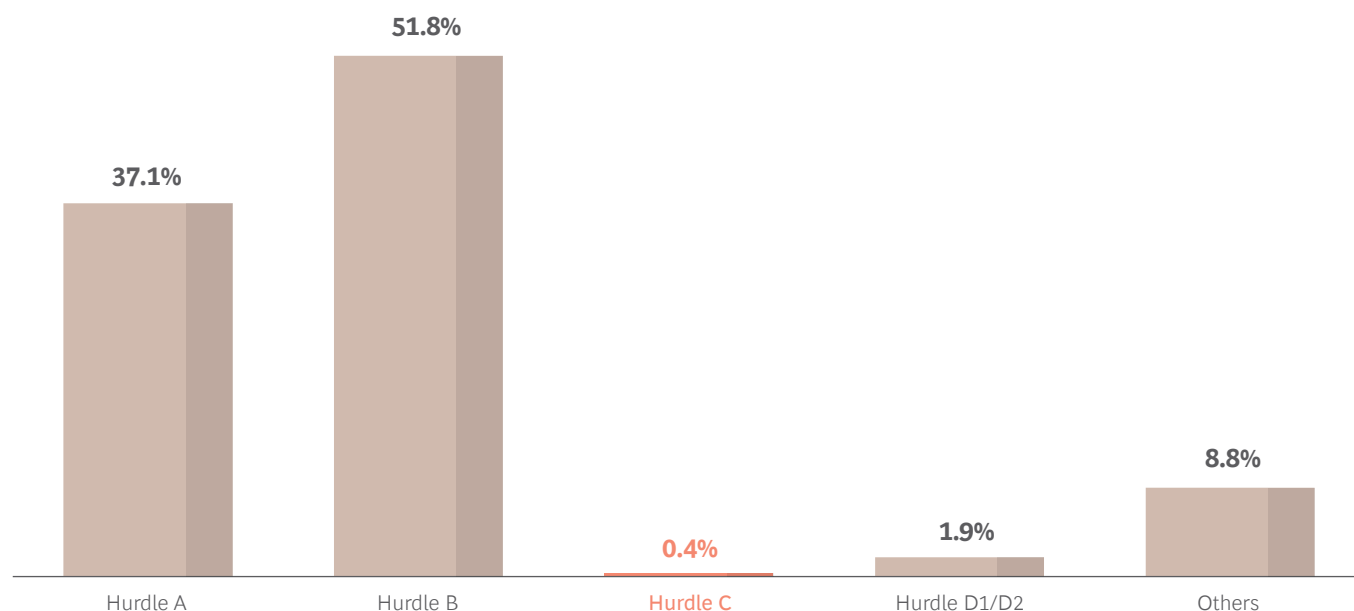


Exhibit 5. Percentage of VC-funded companies focused on each hurdle. In a sample of 838 VC-funded companies, we assessed the focus of activity, with the vast majority focused on hurdles (A) and (B), with very few on hurdle (C).

Our findings are corroborated by others who have found only 5% or less of funding going to companies focused on translational research,^{138,139} with very few startups active on the topic.^{39,126}

The reason for this apparent market failure is that it historically has been difficult or impossible to make the kinds of financial returns from preclinical models (which are sold by the unit) that are available from the development of new modalities (which generally command a royalty stream from any product developed using the modality).^{140,141} This leaves a gap that is also an opportunity that could be addressed in multiple ways.

A private player could exploit this market imperfection by developing better translational models and using them in a proprietary way to pursue drug development with an advantage. A public-private partnership could be developed to deploy the best of industry, academia, and government to create one of these models,¹⁴² analogous to the work of the Accelerating Medicines Project (AMP) on target discovery.¹⁴³ A consortium model could be used, building on nascent efforts at Transcelerate Biopharma's BioCelerate subsidiary.¹⁴⁴ Or government could take on the challenge directly, perhaps building on the National Center for Advancing Translational Sciences's Tissue Chip Testing Centers and related efforts to build better translational models.¹⁴⁵

Concluding Remarks

We have seen the value of applying frameworks such as this one to individual program progression decisions in biopharma, resulting in an upswing in R&D productivity in recent years. It is our hope that applying this thinking at the level of diseases will help drive progress even more broadly by directing efforts in the most fruitful ways to overcome the challenges currently limiting progress in many diseases.

Author Contributions

MSR conceived the analysis; MSR and US oversaw the analysis; JD, MJD, MD, RAF, and SCH gathered data and conducted analyses; MSR and JD drafted the paper; MJD, MD, RAF, SCH, and US edited and approved the paper.

Competing Interests

MSR, JD, and US are employees of Boston Consulting Group (BCG), a management consultancy that works with the world's leading biopharmaceutical companies. MJD, MD, RAF, and SCH are previously employees of BCG. The research for this specific article was funded by BCG's Health Care practice.

MSR is a Bruce Henderson Institute Fellow at Boston Consulting Group, Boston, Massachusetts, USA, email: ringel.michael@bcg.com

JD is at Boston Consulting Group, Washington, D.C., USA

MJD is at Moderna, Cambridge, Massachusetts, USA

MD is at Eisai, Boston, Massachusetts, USA

SCH is at BioNTech US, Cambridge, Massachusetts, USA

US is at Boston Consulting Group, Zurich, Switzerland

1. Dimasi, J.A., Grabowski, J.H. & Hansen, R.W. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J. Health Econ.* **47**, 20-33 (2016).
2. Kola, I. & Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* **3**, 711–715 (2004).
3. Paul, S. M. et al. How to improve R&D productivity: the pharmaceutical industry’s grand challenge. *Nat. Rev. Drug Discov.* **9**, 203–214 (2010).
4. Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nat. Rev. Drug Discov.* **8**, 959–968 (2009).
5. Pammolli, F., Magazzini, L. & Riccaboni, M. The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discov.* **10**, 428–438 (2011).
6. Scannell, J.W., Blanckley, A., Boldon, H. & Warrington, B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* **11**, 191–200 (2012).
7. Ringel, M. S., Scannell, J. W., Baedeker, M. & Schulze, U. Breaking Eroom’s Law. *Nat. Rev. Drug Discov.* **19**, 833–834 (2020).
8. Pammolli, F., et al. The endless frontier? The recent upsurge of R&D productivity in pharmaceuticals. *bioRxiv* (2019).
9. Dimasi, J.A. Assessing pharmaceutical research and development costs. *JAMA Inter. Med.* **178**, 587 (2018).
10. Lendrem, D., Senn, S. J., Lendrem, B. C. & Isaacs, J. D. R&D productivity rides again? *Pharm. Stat.* **14**, 1–3 (2015).
11. Bunnage, M. E. Getting pharmaceutical R&D back on target. *Nat. Chem. Biol.* **7**, 335 (2011).
12. Garnier, J.P. Rebuilding the R&D engine in big pharma. *Harv. Bus. Rev.* **86**, 114 (2008).
13. Wang, L., Plump, A. & Ringel, M.S. Racing to define pharmaceutical R&D external innovation models. *Drug Discov. Today*. **20**, 361–370 (2015).
14. Khanna, I. Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discov. Today* **17**, 1088–1102 (2012).
15. Ringel, M.S., et al. Does size matter in R&D productivity? If not, what does? *Nat. Rev. Drug Discov.* **12**, 901–902 (2013).
16. Peck, R.W. et al. Why is it hard to terminate failing R&D projects in pharmaceutical R&D? *Nat. Rev. Drug Discov.* **14**, 663–664 (2015).
17. Tollman, P., Morieux, Y., Murphy, J. K. & Schulze, U. Identifying R&D outliers. *Nat. Rev. Drug Discov.* **10**, 653 (2011).
18. Owens, P.K. et al. A decade of innovation in pharmaceutical R&D: the Chorus model. *Nat. Rev. Drug Discov.* **14**, 17–28 (2015).
19. Morgan, P. et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov. Today* **17**, 419–424 (2012).
20. Cook, D. et al. Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework. *Nat. Rev. Drug Discov.* **13**, 419–431 (2014).
21. Morgan, P. et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. *Nat. Rev. Drug Discov.* **17**, 167–181 (2018).
22. Wu, et al. Reviving an R&D pipeline: a step change in the Phase II success rate. *Drug Discov. Today* **26**, 308–314 (2021).
23. Plenge, R. M., Scolnick, E. M. & Altshuler, D. Validating therapeutic targets through human genetics. *Nat. Rev. Drug Discov.* **12**, 581–594 (2013).
24. Kingsmore, S.F. et al. Genome-wide association studies: progress and potential for drug discovery and development. *Nat. Rev. Drug Discov.* **7**, 221–230 (2008).
25. Nelson, M.R., et al. The support of human genetic evidence for approved drug indications. *Nat. Gen.* **47**, 856–860 (2015).
26. Chevret, S. (Ed.). *Statistical methods for dose-finding experiments*. Wiley. (2006).
27. Ting, N. & Ting, N. *Dose finding in drug development*. Springer. (2006).
28. Vincent, F., et al. Phenotypic drug discovery: recent successes, lessons learned and new directions. *Nat. Rev. Drug Discov.* 1–16 (2022).
29. Swinney, D. C. & Anthony, J. How were new medicines discovered? *Nat. Rev. Drug Discov.* **10**, 507–519 (2011).
30. Moffat, J. G., Rudolph, J. & Bailey, D. Phenotypic screening in cancer drug discovery—past, present and future. *Nat. Rev. Drug Discov.* **13**, 588–602 (2014).
31. Vincent, F., et al. Developing predictive assays: the phenotypic screening “rule of 3.” *Sci. Trans. Med.* **7**, 293 (2015).
32. Mullard, A. The phenotypic screening pendulum swings: industry and academic scientists are working together to figure out when and how best to use phenotypic screening in drug discovery. *Nat. Rev. Drug Discov.* **14**, 807–810 (2015).

33. Eder, J., Sedrani, R. & Wiesmann, C. The discovery of first-in-class drugs: origins and evolution. *Nat. Rev. Drug Discov.* **13**, 577–587 (2014).
34. Seok, J., et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Nat. Acad. Sci.* **110**, 3507–3512 (2013).
35. Henderson, V. C., et al. Threats to validity in the design and conduct of preclinical efficacy studies: a systematic review of guidelines for in vivo animal experiments. *PLoS Med.* **10**, e1001489 (2013).
36. Honkala, A., Malhotra, S. V., Kummar, S. & Junttila, M. R. Harnessing the predictive power of preclinical models for oncology drug development. *Nat. Rev. Drug Discov.* **21**, 99–114 (2022).
37. Corsini, N. S. & Knoblich, J. A. Human organoids: New strategies and methods for analyzing human development and disease. *Cell.* **185**, 2756–2769 (2022).
38. Butcher, E. C. Can cell systems biology rescue drug discovery? *Nat. Rev. Drug Discov.* **4**, 461–467 (2005).
39. Ewart, L. & Roth, A. Opportunities and challenges with microphysiological systems: a pharma end-user perspective. *Nat. Rev. Drug Discov.* **20**, 327–328 (2021).
40. Fatehullah, A., Tan, S. H. & Barker, N. Organoids as an in vitro model of human development and disease. *Nat. Cell Bio.* **18**, 246–254 (2016).
41. Lamb, J., et al. The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease. *Science.* **313**, 1929–1935 (2006).
42. Subramanian, A., et al. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. *Cell.* **171**, 1437–1452 (2017).
43. McKinney, W., et al. Data structures for statistical computing in python. In *Proceedings of the 9th Python in Science Conference.* **445**, 51–56 (2010).
44. Pedregosa, et al. Scikit-learn: Machine Learning in Python. *JMLR.* **12**, 2825–2830 (2011).
45. Hopkins, A. L. & Groom, C. R. The druggable genome. *Nat. Rev. Drug Discov.* **1**, 727–730 (2002).
46. Russ, A. P. & Lampel, S. The druggable genome: an update. *Drug Discov. Today.* **10**, 1607–1610 (2005).
47. Blundell, T. L. Structure-based drug design. *Nature.* **384**, 23–26 (1996).
48. Ferreira, L. G., Dos Santos, R. N., Oliva, G. & Andricopulo, A. D. Molecular docking and structure-based drug design strategies. *Molecules.* **20**, 13384–13421 (2015).
49. Gehlhaar, D. K., et al. The Pfizer Crystal Structure Database: An essential tool for structure-based design at Pfizer. *J. Comp. Chem.* **43**, 1053–1062 (2022).
50. Polack, F. P., et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *NEJM.* (2020).
51. Jackson, L. A., et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *NEJM.* (2020).
52. Voysey, M., et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *The Lancet* **397**, 881–891 (2021).
53. Sadoff, J., et al. Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19. *NEJM.* **384**, 2187–2201 (2021).
54. Levin, M. J., et al. Intramuscular AZD7442 (tixagevimab–cilgavimab) for prevention of COVID-19. *NEJM.* (2022).
55. Gupta, A., et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *NEJM.* **385**, 1941–1950 (2021).
56. Westendorf, K., et al. LY-CoV1404 (bebtelovimab) potentially neutralizes SARS-CoV-2 variants. *Cell Reports.* **39**, 110812 (2022).
57. Dougan, M., et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *NEJM.* **385**, 1382–1392 (2021).
58. Razonable, R. R., et al. Casirivimab–Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19. *E Clin. Med.* **40**, 101102 (2021).
59. Heath, P. T., et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *NEJM.* **385**, 1172–1183 (2021).
60. Beigel, J. H., et al. Remdesivir for the treatment of Covid-19. *NEJM.* **383**, 1813–1826 (2020).
61. Group, T. R. C. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *NEJM.* (2020).
62. Jayk Bernal, A., et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *NEJM.* **386**, 509–520 (2022).
63. Cantini, F., et al. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *J. Infect.*, **81**, 318–356 (2020).
64. Hammond, J., et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *NEJM.* **386**, 1397–1408 (2022).

65. Ecker, D. M., Jones, S. D. & Levine, H. L. The therapeutic monoclonal antibody market. *MAbs* **7**, 9–14 (2014).
66. Liu, J. K. H. The history of monoclonal antibody development - Progress, remaining challenges and future innovations. *Ann. Med. Surg.* **3**, 113–116 (2014).
67. Reichert, J. Monoclonal Antibodies as Innovative Therapeutics. *Curr. Pharm. Biotechnol.* **9**, 423–430 (2008).
68. Ndoja, S. & Lima, H. 4 - Monoclonal Antibodies. in (eds. Thomaz-Soccol, V., Pandey, A. & Resende, R. R. B. T. C. D. in B. and B.) 71–95 (Elsevier, 2017). doi:<https://doi.org/10.1016/B978-0-444-63660-7.00004-8>.
69. Geskin, L. J. Monoclonal Antibodies. *Dermatol. Clin.* **33**, 777–786 (2015).
70. Salmaninejad, A. et al. Duchenne muscular dystrophy: an updated review of common available therapies. *Int. J. Neurosci.* **128**, 854–864 (2018).
71. Gawlik, K. I. At the crossroads of clinical and preclinical research for muscular dystrophy—are we closer to effective treatment for patients? *Int. J. Mol. Sci.* **19** (2018).
72. Strehle, E. M. & Straub, V. Recent advances in the management of Duchenne muscular dystrophy. *Arch. Dis. Child.* **100**, 1173–1177 (2015).
73. Bulfield, G., Siller, W. G., Wight, P. A. & Moore, K. J. X chromosome-linked muscular dystrophy (mdx) in the mouse. *Proc. Natl. Acad. Sci.* **81**, 1189–1192 (1984).
74. Lim, K. R., Maruyama, R. & Yokota, T. Eteplirsen in the treatment of Duchenne muscular dystrophy. *Drug Des. Dev. Ther.* **11**, 533–545 (2017).
75. Aartsma-Rus, A. & Goemans, N. A Sequel to the eteplirsen saga: Eteplirsen is approved in the United States but was not approved in Europe. *Nucleic Acid Ther.* **29**, 13–15 (2019).
76. FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation. Food and Drug Administration Web site. <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation>. Accessed January 13, 2023.
77. Dhillon, S. Viltolarsen: First approval. *Drugs*. **80**, 1027–1031 (2020).
78. FDA approves targeted treatment for rare Duchenne Muscular Dystrophy mutation. Food and Drug Administration web site. <https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0>. Accessed January 13, 2023.
79. DisGeNET web site. <https://www.disgenet.org/browser/0/1/0/C2717906/>. Accessed January 13, 2023.
80. Han, E. D., et al. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J. Clin. Invest.* **109**, 1057–1063 (2002).
81. Bupp, S., et al. A novel murine in vivo model for acute hereditary angioedema attacks. *Sci. Rep.* **11**, 15924 (2021).
82. Caballero, T. Treatment of hereditary angioedema. *J. Invest. Aller. Clin. Immunol.* **31**, 1–16 (2021).
83. Caballero, T., et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part I. Classification, epidemiology, pathophysiology, genetics, clinical symptoms, and diagnosis. *J. Invest. Aller. Clin. Immunol.* **21**, 333–347 (2011).
84. Maurer, M., et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2017 revision and update. *Allergy*. **73**, 1575–96 (2018).
85. Betschel, S., et al. The international/Canadian hereditary angioedema guideline. *Allergy Asthma Clin. Immunol.* **15**, 72 (2019).
86. Company pipeline, KalVista, 19 May 2022, <https://www.kalvista.com/products-pipeline>.
87. Company pipeline, Ionis, 25 Oct 2017 & 22 Sep 2021, <https://www.ionispharma.com/ionis-innovation/pipeline>.
88. Company pipeline, 7 Jun 2019, <https://www.csl.com/en-us/research-and-development/product-pipeline>.
89. Oseini, A. M. & Sanyal, A. J. Therapies in non-alcoholic steatohepatitis (NASH). *Liver Int.* **37** Suppl 1, 97–103 (2017).
90. Benedict, M. & Zhang, X. Non-alcoholic fatty liver disease: An expanded review. *World J. Hepatol.* **9**, 715–732 (2017).
91. Lau, J. K. C., Zhang, X. & Yu, J. Animal models of non-alcoholic fatty liver disease: current perspectives and recent advances. *J. Pathol.* **241**, 36–44 (2017).
92. Weltman, M. D., Farrell, G. C. & Liddle, C. Increased Hepatocyte CYP2E1 Expression in a Rat Nutritional Model of Hepatic Steatosis With Inflammation. *Gastroenterology* 1645–1653 (1996).
93. Van Herck, M. A., Vonghia, L. & Francque, S. M. Animal Models of Nonalcoholic Fatty Liver Disease—A Starter’s Guide. *Nutrients* **9**, 1072 (2017).
94. Benedict, M. & Zhang, X. Non-alcoholic fatty liver disease: An expanded review. *World J. Hepatol.* **9**, 715–732 (2017).
95. Chalasani, N. et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* **67**, 328–357 (2018).

96. Manns, M. P. et al. Hepatitis C virus infection. *Nat. Rev. Dis. Prim.* **3**, 17006 (2017).
97. Kuo, G. et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science*. **244**, 362 LP-364 (1989).
98. Alter, H. Discovery of non-A, non-B hepatitis and identification of its etiology. *Am. J. Med.* **107**, 16–20 (1999).
99. Nishizono, A. et al. Correlation of serum antibody titers against hepatitis C virus core protein with clinical features by western blot (immunoblot) analysis using a recombinant vaccinia virus expression system. *J. Clin. Microbiol.* **31**, 1173–1178 (1993).
100. Selby, M. J., et al. Expression, identification and subcellular localization of the proteins encoded by the hepatitis C viral genome. *J. Gen. Virol.* **74**, 1103–1113 (1993).
101. Feld, J. J. & Hoofnagle, J. H. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* **436**, 967 (2005).
102. Rong, L. & Perelson, A. S. Treatment of Hepatitis C Virus Infection With Interferon and Small Molecule Direct Antivirals: Viral Kinetics and Modeling. *Crit. Rev. Immunol.* **30**, 131–148 (2010).
103. Lohmann, V. et al. Replication of Subgenomic Hepatitis C Virus RNAs in a Hepatoma Cell Line. *Science*. **285**, 110 LP-113 (1999).
104. Zhu, Q. et al. Novel Robust Hepatitis C Virus Mouse Efficacy Model. *Antimicrob. Agents Chemother.* **50**, 3260–3268 (2006).
105. American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). Recommendations for testing, management, and treating hepatitis C: HCV testing and linkage to care. Available at: <https://www.hcvguidelines.org>.
106. Vandamme, T. F. Use of rodents as models of human diseases. *J. Pharm. Bioallied Sci.* **6**, 2 (2014).
107. van der Worp, H. B. et al. Can Animal Models of Disease Reliably Inform Human Studies? *PLOS Med.* **7**, e1000245 (2010).
108. Kiebertz, K. & Olanow, C. W. Translational experimental therapeutics: The translation of laboratory-based discovery into disease-related therapy. *Mt. Sinai J. Med. A J. Transl. Pers. Med.* **74**, 7–14 (2007).
109. Ringel, M. S., et al. Occlusion in the flow of new drugs for cardiovascular disease. *Clin. Pharm. & Ther.* **102**, 246–253 (2017).
110. Bush, W. S., Oetjens, M. T. & Crawford, D. C. Unravelling the human genome–phenome relationship using phenome-wide association studies. *Nat. Rev. Genet.* **17**, 129–145. (2016).
111. FitzGerald, G., et al. The future of humans as model organisms. *Science*. **361**, 552–553 (2018).
112. Kramer, R. & Cohen, D. Functional genomics to new drug targets. *Nat. Rev. Drug Discov.* **3**, 965–972 (2004).
113. Mullard, A. Hal Barron. *Nat. Rev. Drug Discov.* **18**, 166–168 (2019).
114. Claussnitzer, M., et al. A brief history of human disease genetics. *Nature*. **577**, 179–189 (2020).
115. Visscher, P. M., et al. 10 years of GWAS discovery: biology, function, and translation. *Am. J. Human Genet.* **101**, 5–22 (2017).
116. Burt, T., et al. Phase 0/microdosing approaches: time for mainstream application in drug development? *Nat. Rev. Drug Discov.* **19**, 801–818 (2020).
117. Scannell, J. W., et al. Predictive validity in drug discovery: what it is, why it matters and how to improve it. *Nat. Rev. Drug Discov.* 1–17 (2022).
118. Scannell, J. W. & Bosley, J. When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One*. **11**, e0147215 (2016).
119. <https://en.wikipedia.org/wiki/Homunculus>, retrieved 11 January 2023.
120. Takebe, T. & Wells, J. M. Organoids by design. *Science*. **364**, 956–959 (2019).
121. Sato, T. Novel intestinal stem cell culture system. *Inflam. and Regen.* **32**, 43–47 (2012).
122. Sato, T., et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*. **459**, 262–265 (2009).
123. Low, L. A., et al. Organs-on-chips: into the next decade. *Nat. Rev. Drug Discov.* **20**, 345–361 (2021).
124. Esch, E. W., Bahinski, A. & Huh, D. Organs-on-chips at the frontiers of drug discovery. *Nat. Rev. Drug Discov.* **14**, 248–260 (2015).
125. Park, S. E., Georgescu, A. & Huh, D. Organoids-on-a-chip. *Science*. **364**, 960–965 (2019).
126. Vunjak-Novakovic, G., Ronaldson-Bouchard, K. & Radisic, M. Organs-on-a-chip models for biological research. *Cell*. **184**, 4597–4611 (2021).
127. Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. **126**, 663–676 (2006).

128. Grskovic, M., Javaherian, A., Strulovici, B. & Daley, G. Q. Induced pluripotent stem cells—opportunities for disease modelling and drug discovery. *Nat. Rev. Drug Discov.* **10**, 915–929 (2011).
129. Powley, I. R., et al. Patient-derived explants (PDEs) as a powerful preclinical platform for anti-cancer drug and biomarker discovery. *Brit. J. Cancer.* **122**, 735–744 (2020).
130. Dönertaş, H. M., Fuentealba, M., Partridge, L. & Thornton, J. M. Identifying potential ageing-modulating drugs in silico. *Trends Endocrin. & Met.* **30**, 118–131 (2019).
131. Xu, J., et al. Interpretable deep learning translation of GWAS and multi-omics findings to identify pathobiology and drug repurposing in Alzheimer’s disease. *Cell Reports.* **41**, 111717 (2022).
132. McLoughlin, K. S., et al. Machine learning models to predict inhibition of the bile salt export pump. *J. Chem. Info. & Model.* **61**, 587–602 (2021).
133. Horvath, P., et al. Screening out irrelevant cell-based models of disease. *Nat. Rev. Drug Discov.* **15**, 751–769 (2016).
134. Wieschowski, S., et al. Preclinical efficacy studies in investigator brochures: do they enable risk–benefit assessment? *PLoS Bio.* **16**, e2004879 (2018).
135. Pound, P. & Bracken, M. B. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ.* **348** (2014).
136. Pound, P., et al. Where is the evidence that animal research benefits humans? *BMJ.* **328**, 514–517 (2004).
137. Ioannidis, J. P. Extrapolating from animals to humans. *Sci. Trans. Med.* **4**, 151ps15. (2012).
138. Dickman, S. Investing in translational research to produce clinical, commercial and financial outcomes: Current and future mechanisms. *A White Pap. CIRM by Steve Dickman team CBT Advis.* 1–46 (2013).
139. Milken Innovation Center. FIXES IN FINANCING Financial Innovations for Translational Research. *A Financ. Innov. LAB Rep.* (2012).
140. Zuberi, A. & Lutz, C. Mouse models for drug discovery. Can new tools and technology improve translational power? *ILAR J.* **57**, 178–185 (2016).
141. Seymore, S. B. Making Patents Useful. *Minn. L. Rev.* **98**, 1046 (2013).
142. Said, M. & Zerhouni, E. The role of public–private partnerships in addressing the biomedical innovation challenge. *Nat. Rev. Drug Discov.* **13**, 789–790 (2014).
143. Mullard, A. Drug makers and NIH team up to find and validate targets: the \$230 million AMP stakes out new target ground in Alzheimer’s disease, type 2 diabetes, rheumatoid arthritis and lupus. *Nat. Rev. Drug Discov.* **13**, 241–244 (2014).
144. Mullard, A. TransCelerate makes progress. *Nat. Rev. Drug Discov.* **16**, 229–230 (2017).
145. Willyard, C. Channeling chip power: Tissue chips are being put to the test by industry. *Nat. Med.* **23**, 138–141 (2017).

About the Authors

Michael S. Ringel is a Managing Director and Senior Partner at Boston Consulting Group and Bruce Henderson Institute Fellow for Growth and Innovation. You may contact him by email: ringel.michael@bcg.com.

Ulrik Schulze is a Managing Director and Senior Partner at Boston Consulting Group, and leads BCG's Health Care Practice in Switzerland.

Julie Dethier is a Principal at Boston Consulting Group, with a strong background in global health, public sector, and biopharmaceuticals.

Michelle J. Davitt is a Boston Consulting Group Alumnus and most recently at Moderna.

Maria Denslow is a Boston Consulting Group Alumnus and is currently a Senior Director of External Innovation at Eisai.

R. Andrew Fowler is a Boston Consulting Group Alumnus.

Sebastian C. Hasenfuss is a Boston Consulting Group Alumnus and is currently a Director, Corporate Strategy, at BioNTech US.

For Further Contact

If you would like to discuss this report, please contact the authors.

Boston Consulting Group partners with leaders in business and society to tackle their most important challenges and capture their greatest opportunities. BCG was the pioneer in business strategy when it was founded in 1963. Today, we work closely with clients to embrace a transformational approach aimed at benefiting all stakeholders—empowering organizations to grow, build sustainable competitive advantage, and drive positive societal impact.

Our diverse, global teams bring deep industry and functional expertise and a range of perspectives that question the status quo and spark change. BCG delivers solutions through leading-edge management consulting, technology and design, and corporate and digital ventures. We work in a uniquely collaborative model across the firm and throughout all levels of the client organization, fueled by the goal of helping our clients thrive and enabling them to make the world a better place.

For information or permission to reprint, please contact BCG at permissions@bcg.com. To find the latest BCG content and register to receive e-alerts on this topic or others, please visit [bcg.com](https://www.bcg.com). Follow Boston Consulting Group on [Facebook](#) and [Twitter](#).

© Boston Consulting Group 2023. All rights reserved. 6/23

