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Reproducibility, Relevance and Reliability as Barriers to Efficient and Credible Biomedical Technology Translation

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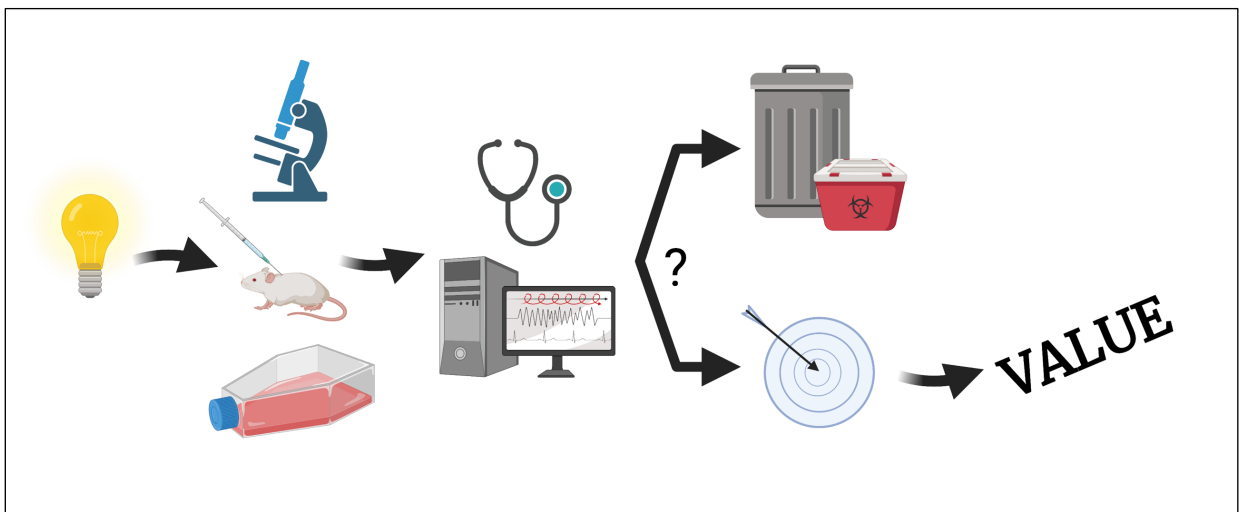
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ToC Graphic:

> *"Knowing is not enough; we must apply. Willing is not enough; we must do."*
> J.W v. Goethe

Abstract:

Biomedical research accuracy and relevance for improving healthcare are increasingly identified as costly problems. Basic research data quality, reporting and methodology, and reproducibility are common factors implicated in this challenge. Preclinical models of disease and therapy, largely conducted in rodents, have known deficiencies in replicating most human conditions. Their translation to human results is acknowledged to be poor for decades. Clinical data quality and quantity is also recognized as deficient; gold standard randomized clinical trials are expensive. Few solid conclusions from clinical studies are replicable and many remain unpublished. The translational pathway from fundamental biomedical research through to innovative solutions handed to clinical practitioners is therefore highly inefficient and costly in terms of wasted resources, early claims from fundamental discoveries never witnessed in humans, and few new, improved solutions available clinically for myriad diseases. Improving this biomedical research strategy and resourcing for reliability, translational relevance, reproducibility and clinical impact requires careful analysis and consistent enforcement at both funding and peer review levels.

1. Introduction

Translation of biomedical research results into clinical benefits is the rallying cry of the modern medical research establishment [1]. Medical innovation is linked to effective translation of new discoveries about disease, and in how drugs and devices produce therapies. Many challenges are commonly identified in translating observations from model experimental biomedical research systems (e.g., *in silico, in vitro, ex vivo,* or *in vivo* in animal preclinical studies) towards treatments of human diseases and improvement of clinical practices [2–9]. Myriad murine disease models are frequently used to herald new "cures" for diverse human diseases, that unfortunately for most, prove to be invalid [10,11]. Only a small fraction of animal study outcomes are deemed transferrable to relevant human responses, thus qualifying as "knowledge-gaining research" [12]. The remainder often claim "potential" relevance, yet are poorly convincing, unsupported, or too risky or ambiguous to attempt correlation or translation to human conditions, and without clear clinical impact. This widely recognized but worrisome chasm separating discovery from technology validation and clinical

74 impact de-values the role and credibility of the biomedical scientist and erodes their contributions to

75 addressing compelling healthcare challenges [13,14].

76

77 A sound understanding of the medical need, its underlying causes and consequences, and whether

78 corresponding preclinical data are likely to be clinically relevant, appear necessary to confidently

79 proceed from preclinical to clinical testing for validation. Accurate and validated scientific evidence

80 generated in a timely manner in relevant biomedical research testbeds is required to address unmet

81 needs and also the divides between biomedical research and clinical challenges. "Translation" is

82 defined as the essential process of turning observations in the laboratory, clinic and community into

83 new interventions that improve both the health of individuals and the public — from diagnostics and

84 therapeutics to medical procedures and behavioral changes [15]. Nonetheless, formidable barriers

85 are frequently recognized that preclude ready achievement of this mission [16]. Traditionally,

86 distinctions in translational cultures among investigators, regulatory hurdles, limited data access,

87 reproducibility, usability, and poorly predictive research models have been identified [17]. Practically,

88 a critical barrier surrounds the increasing complexity of biomedical information and limited research

89 capabilities to integrate complex multi-factorial data across multiple research formats. Research

90 strategies to effectively and comprehensively accommodate complex, dynamic models of health,

91 disease and intervention do not yet exist in many cases.

92

2. Predicting Translational Success

94 A particularly acute facet of the translational research challenge is evident in the depressingly low rate

95 of successful translation of preclinical models to human experiences [16,18–21]. Years ago, a

96 systematic review identified that only about a third of 67 highly cited animal research studies could

97 translate accurately at the level of published human randomized trials [22]. Translational

98 predictiveness and reliability shown in that study is poorer than the recently estimated replication

99 rates, less reliable than a coin toss, for highly cited human studies [23,24]. Given these precarious

100 features of translational science, extrapolating outcomes from animal research as models of human

101 maladies into claims for approaches to treating human disease should be performed with caution [25].

102 These noted deficiencies certainly provide major opportunities for improving study design and

103 methodological quality for preclinical research that might improve human relevance.

104

> *"The definition of insanity is doing the same thing over and over again, but expecting different results."*
>
> (attributed to 1981 *Narcotics Anonymous* pamphlet)

2.1 Changing Decades of Habit

To produce different, and better, results than those published, the research community must attempt different methodologies and approaches. Over 26 years ago, Altman asserted, "We need less research, better research, and research done for the right reasons"[26]. Yet, scientists like all other humans are creatures of routine who respond naturally to the incentives provided for performance: *it is constantly* challenging *to expect, develop and enforce different and hopefully improved, validated approaches to address long-standing challenges, particularly in medical research centered on humans.* One prominent hindrance is the dominant, pervasive incentive system for scientific recognition, promotion and success in academic research, relying on impact-agnostic numerical compilations and assessments of scholarly production [27–31]. Indeed, pet academic performance analytical tools now commonly employed by university administrative rankings and assessments use publications as "a currency they were never meant to be: a system of metrics to assess research, research programs and individual researchers" [32]. These research performance constraints perpetuate the long-standing insidious academic "publish-or-perish" culture, engaging 15,000,000 researchers publishing over 25,000,000 scientific papers in 1996–2011 alone [33], without much incentive to change either the metrics, merits, or the results. Furthermore, the audience for this mass of "discovery" literature is unappreciative and inattentive: the 10-year uncited rate for publications across all science disciplines, minus self-citation, is about 18% [34]. This excessive and under-appreciated global dissemination effort is openly acknowledged as a costly system that fails all involved in bringing the expected academic learnings, progress, innovation and research breakthroughs to benefit society. Nonetheless, when "researchers are rewarded primarily for publishing, then habits which promote publication are naturally selected…. they modify their methods to produce the largest possible number of publishable results rather than the most rigorous investigations" [29]. Enormously profitable scientific publishing business interests [35] and the dubious roles of researchers as both the producers and consumers in this publication business (and who pay in both roles) introduce orthogonal pressures on research systems as well. New, unanticipated consequences and unfiltered media hype, often through rapid social media dissemination of non-factual reports and non-peer reviewed evidence [36] produce new complexities for scientific accuracy. Breaking this performance pattern, removing the perverse incentives from for-profit external forces [27–31] and restoring biomedical research to originally envisioned more altruistic and impacting goals beyond publications will require concerted will and

136 dedication from numerous stakeholders [30,37,38]. Publications are important dissimenation tools as
137 critical reports of progress to their stakeholders, but these are not final products [32,37]. Publishers
138 and journal editorial boards could wield increasing influence in setting standards for acceptable
139 research conduct and quality [39]. Researchers themselves, along with their peers and administrators
140 who supervise the promotional and merti-review/reward systems, along with funding agencies that
141 promote research programs with little hope for progress by relying on failed research tools and
142 irrelevant disease models, and finally the peer-review community that seemingly condones the
143 exaggerations of novelty and claims of impact while perpetuating certain systemic futility and wasted
144 resources through their approval of compromised models, poor strategies and faulty techniques, must
145 all be called upon to implement change.

146

147 ### *2.2 Addressing Preclinical Failure*

148 Using previous publications uncritically to justify further *in vivo* work, regardless of their veracity,
149 relevance, robustness or quality, is often the most rapid route to institutional animal study approval
150 and to obtaining publishable data, even though these data may have no translational relevance.
151 Furthermore, a substantial fraction of these studies suffer from poor experimental design and
152 methodological flaws, often under cost and funding constraints. Under-powered animal studies, long
153 known to be the bane of preclinical translational reliability [40–42], continue to be published and
154 accepted as valid whole organism in vivo outcomes, despite poor methodological design [21,43], lack
155 of validation and low or no human relevance. However, apparently exciting preclinical data may fail
156 to translate to the next step at many levels and for many reasons (Table 1) [2,10,18,21,43].

157

158 **Table 1**. Some examples of failure of translation of preclinical disease models to human trials.

Disease Model	Example of failure of translation
Inflammatory arthritis, lupus, other autoimmune diseases	>20 p38 inhibitors failed in clinic [44]
Vascular prosthetic graft placement and endothelialization	Success in models fails to predict clinical benefit [45]
Various cancer models	Success in models fails to predict clinical benefit [46]
Various pain models	Success in models fails to predict clinical benefit [47,48]
Various stroke models	Success in models fails to predict clinical benefit [49,50]

6

In vivo cell and gene therapies in highly inbred, specialized mouse strains	Success in models fails to duplicate human experiences [51]
Various osteoarthritis models	Success in models falls short in predicting clinical effects [52,53]

Given abundant questioning and critique published for many current animal models used in biomedical research, criteria for defining validity of improved animal models is essential, and refining best practies for their adoption and continual evolution should be a research community mandate [54,55]. Some experimental uncertainties in models are certainly outside the researchers' control – biology is indeed complex, often exhibiting non-linear or quasi-chaotic dynamics, and difficult to model. The biology may simply differ in humans compared to model systems or non-human animals. In these cases, research model pursuit can be justified in terms other than direct one-to-one human relevance, such as isolating a specific relevant mechanistic signal, elucidating a relevant pathway, or assessing genetic contribution. Some argue that external validity (translation to other laboratories running similar experiments, in other study populations, or other species) as well as internal validity (competent experimental design, expert conduct and analysis, and accurate reporting) are both essential, and that reliable translation of research results from animal models to humans can only occur if preclinical animal studies are both internally and externally valid [56,57].

> *"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives, the cumulative experience of many masters…"*
>
> William A. Foster

3. Reproducibility and Robustness

3.1 Internal Validity

Reproducibility and robustness (internal validity) are the bedrock of science and as such, also essential for biomedical translation [58]. Meta-research of the past decade has provided overwhelming evidence that research of low internal validity and statistical power is a major cause of translational attrition. For example, a recent analysis of 1.6 million papers (1997–2019) quantifying the rigor and transparency in the reporting of preclinical research demonstrated that less than 30% of studies mention methods to reduce bias (blinding, randomization, etc.) [59]. Average statistical power in most work appears to be below 10%. As a consequence, false positive as well as false negative results

183 abound, and even where effects are real, their effect sizes may be substantially overestimated

184 [22,30,60]. Predominant reliance of the biomedical field on null hypothesis significance testing (NHST),

185 and associated use and misuse of *P* values for validation [40–42] is argued to now be the "most widely

186 perpetrated misdeed of statistical inference across all of science" [61]. Selection bias, p-hacking, and

187 data cherry-picking are common modalities used to falsely assert statistical validity for study

188 conclusions. Proper application of effect sizes, confidence intervals, techniques analyzing false

189 discovery rates, Bayesian methods, and adoption of more stringent thresholds for asserting *P* values

190 are all proposed alternatives to avoiding these increasingly reported questionable practices that

191 plague experimental reproducibility and data robustness [29,30,58].

192

193

3.2 External validity

195 In addition, generalizability (i.e., external validity) is significant to translational success and reliability.

196 How well the chosen research model reflects critical factors of a relevant clinical setting is key to

197 recapitulating disease pathophysiology, and hence for validating outcomes for possible therapeutic

198 predictions. This includes – but is not limited - to sex, age, immune system status, microbiome, etc, as

199 modifiers of an adequate model [62]. In-depth knowledge of the patient-specific medical need, its

200 physiological and pathological characteristics and variation is essential. Recently it was proposed that,

201 quite counterintuitively, experimental heterogeneity should be more widely embraced to improve

202 model reproducibility and translatability. Instead of increasing reproducibility, the current emphasis

203 on experimental standardization may actually reduce variability within studies and lead to

204 idiosyncratic, lab-specific results that are not generally reproducible or translatable [63]. Therefore,

205 activities to deliberately introduce heterogeneity (i.e., "heterogenization") into the experimental

206 design may lead to higher success in drug discovery or medtech developments and their later

207 translation.

208

209 The translatability of preclinical models in reliably predicting human results varies dramatically by

210 disease. In many diseases, the primary animal model has been "cured" many times without leading to

211 a successful human therapy or mitigation (e.g., the *mdx* mouse of Duchenne muscular dystrophy [64],

212 the EAE-model of multiple sclerosis [65], different animal models for infections and sepsis [66,67],

213 various animal models for tolerance induction in solid organ transplantation [68], hundreds of diverse

214 refractory murine tumor types [46]), while other unmet needs manifest better predictivity

215 (inflammatory arthritis models predicting efficacy of TNF inhibitors for rheumatoid arthritis [52,53,69],

216 estrogen withdrawal for osteoporosis [70], immunotherapies involving checkpoint inhibitors and CAR-

217 T cells in liquid tumors), even though the animal model might share few features closely associated

218 with the human disease (e.g., few mammals progress naturally to osteoporosis [71] or spontaneously

'The best material model of a cat is another, or preferably the same, cat.'
(Norbert Wiener, with A. Rosenblueth, Philosophy of Science 1945)

219 develop tumors as in humans [46]).

220

3.3 The End of the Animal Model?

222 Additional data to test a hypothesis before proceeding to human trials ideally should be orthogonally

223 designed – preferably from genetic validation in humans, or from inferential human evidence such as

224 "real world" data, related known pathway interventions by other human drugs, etc. *We contend that*

225 *spending time, effort and money to create new models seeking closer preclinical relationships or*

226 *equivalence to human disease is not an efficient use of research resources.* After all, most animal

227 models have recognized limitations that may never duplicate any human disease entirely [18–22,46]

228 – and importantly, need not be [19,43]. Animal models have utility for only select aspects of

229 biomedical research validation and confirmation, often limited mechanistic acute pharmacological,

230 toxicological, or biomechanical features. Human translational forecasting should not and cannot rely

231 on such limitations. Yet, there does not appear to be the resolve in the research community to

232 understand, directly address and alter many of the current challenges in translating animal results to

233 human use: reviews and summaries of evidence from animal research are methodologically

234 inadequate [72], and few animal study meta-analyses are conducted compared to clinical trial meta-

235 analyses [20,43].

236

237 For biopharmaceutical industry, it is much more effective to proceed to human testing as rapidly as

238 possible once some preclinical evidence of benefit is obtained in a model that has demonstrable

239 perturbation of the target pathway that is substantially corrected by the candidate therapy under

240 investigation. Companies are generally willing to test the hypothesis in the most relevant species –

241 humans – after proving basic, necessary pharmacological and toxicological features in preclinical

242 models. Predictive pathologic pathway mechanistic information is more insightful in preclinical testing

243 that actually establishing complete animal-human disease or healing equivalence. Ironically,

244 toxicology studies needed for human trials are uniformly done in healthy animals, not in disease

245 models. To that end, different critical questions must be answered – safety, tolerability, dosing, effect

246 size, biomarkers – that do not require more basic experiments with disease models. This also means

247 that additional attention and resources are needed to safely and ethically facilitate the human-tissue

248 and human experience-based data that often fall under the rubric of "translational research" [3,6,8–

249 10].

250

4 Regulators, Clinical Trials and Academia: Worlds Apart

252 The traditional world of fundamental and applied research is dominated by academic centers, while

253 later testing of therapeutic candidates is performed primarily by industry, with academic contributions

254 to industry-sponsored clinical trials or investigator-initiated trials. The latter space has formal and

255 continuous regulatory oversight from health authorities, while the former is generally regulated only

256 by animal use committees and funding reviews. New advanced therapies (i.e., cell and gene therapies,

257 tissue engineering, medical technologies, and their combinations) have closed the gap between the

258 regulatory world and the academic world, as many clinical developments in this field are driven by

259 academic labs, with many new regulatory challenges [73]. If this trend is to continue, then educating

260 young researchers with a mindset targeted towards the basics of translational medicine and important

261 regulatory realities will also be necessary [74,75]. In addition, the active development bridge between

262 idea-generating fundamental research and the subsequent regulated clinical development can

263 accelerate and de-risk translation if high standards of quality are maintained in this transition phase

264 [3,75].

265

266 Reproducibility, veracity and validity of early mechanistic therapeutic data comprise the foundation

267 upon which the entire edifice of clinical research is built. All new medicines, interventions and

268 treatments results from volunteers participating in clinical trials. In clinical research, trials are

269 conducted using recruited, screened patient volunteers to answer patient-related questions, and are

270 required by governmental regulatory bodies as the basis for generating evidence for approval

271 decisions. Randomized controlled trials (RCTs) are considered the gold-standard trial format, and

272 optimal approach to study both safety and efficacy of new treatments: trial design processes to

273 conduct an RCT minimize risks from confounding factors that might influence outcomes. As a result,

274 RCTs are widely encouraged as the ideal methodology for causal inference and estimates of average

275 treatment effects. Together with meta-analyses of pooled clinical trial data, high-quality RCTs with a

276 low risk of systematic error (bias) provide the highest level of medical evidence. Analogous to other

277 forms of biomedical research (*vida supra*) arguments relevant to their external and internal validity

278 considerations are published [76].

279

280 While RCTs may be considered the gold standard for generating clinical evidence, they are expensive,
281 time-consuming, lengthy, tedious and difficult. Clinical research also has questionable quality,
282 reliability and replicability challenges [24,33,77]. Because clinical acceptance, patient safety and
283 treatment efficacy, and further research designs all depend directly on conclusions drawn from clinical
284 research, and meta-analysis quality is intrinsically dependent on clinical trial evidence quality, clinical
285 research reliability and veracity is essential. Interestingly, much of modern medical practice and
286 established routine is not based on RCT vetting, as clinical medicine relies primarily on empirically
287 "grandfathered" best practices and anecdotes collected and established from centuries of
288 observational evidence. Hence, there is a growing interest in using real-world evidence (RWE). RWE is
289 proposed to avoid the patient exclusion criteria used in RCTs, and to better reflect actual patient
290 demographics, co-morbidities, protocol adherence, and concurrent treatment use in actual clinical
291 environments, However, only a small fraction of RCTs are replicated to date in the real world [78] and
292 these are typically using retrospective (observational) RWE patient data.

293

294 Regardless of clinical trial design and conduct, an essential contribution of clinical trial data comes
295 from reliable trial conduct, including results reporting. This expectation is enforced by regulatory
296 bodies to make detailed information regarding testing and evaluation of regulated products available
297 to the public to support trial enrollment, inform clinical care decisions, and accelerate future
298 research. Despite nearly 275,000 clinical trials registered on ClinicalTrials.gov currently, fewer than
299 10% of these trials report results publicly to the site annually. Less than half of all clinical trial results
300 have ever been published [79]. Further, less than half of NIH-sponsored clinical trials are published in
301 peer-reviewed journals within 30 months of trial completion [80,81]. Thousands of USA-conducted
302 clinical trials are identified as noncompliant with regulatory results information reporting
303 requirements as of January 2021. The regulatory (and often funding agency) requirement and
304 expectations that public recruitment and involvement in clinical research should be reported publicly
305 in a timely manner has recently begun to be enforced [82].

306

307 Ironically, clinical trials with positive results are twice as likely to be published as those with negative
308 results [79,83]. Trials evaluating treatments of chronic medical conditions published early in the chain
309 of evidence commonly demonstrate an exaggerated treatment effect compared with subsequent
310 trials [84]. In over a third of clinical studies analyzed, first or second clinical trial study otucomes
311 reported an effect 2.67 times larger than what subsequent trials eventually showed. Further, clinical
312 trial data from small clinical trials published in major general medical journals exhibit more
313 exaggerated results overall than equivalent studies published in other journals [85]. Trial results are

314 most often published in English, and the likelihood of publication is frequently decoupled from sample
315 size, funding mechanism, investigator rank or gender [86]. The notable lack of normal and consistent
316 publication practices represents a significant publication bias, and one in this case that is highly
317 unpredictable and non-uniform.

318

319 Unfortunately, scientific research validity is seriously threatened by such publication bias. Decision-
320 making for clinical innovations based on studies showing exaggerated benefit, or biased by lack of
321 studies published showing adverse effects, provides very low certainty in such recommendations [83].
322 Further, clincial data meta-analyses are more likely to consider more trial reports with positive findings
323 than with negative findings, and the estimated pooled effect size is likely to be exaggerated from
324 publication bias. Resulting clinical recommendations based on such evidence influenced by
325 publication bias falls victim to likely exaggerated benefits. Therefore, fair assessment of patient
326 benefit and harm producing such recommendations is likely inaccurate. This risk is acknowledged in
327 clinical trial assessments by reducing certainty in the quality of the evidence provided [87].

328

329 Today, the success rate of translation is woefully low – even among drugs that enter phase I human
330 trials, fewer than 10% are eventually registered as new drugs, often after costly failed trials
331 [6,9,10,88]. Given the known limitations of preclinical models discussed above, it is critical to learn as
332 much as possible in early clinical trials using accompanying mechanistic studies (safety, PD/PK, mode-
333 of-action, surrogate markers). Given that the proportion of early trial failure due to safety versus
334 efficacy is likely roughly equal, and not frequently posted to clinical registries, reliable results from
335 those studies require highly validated biomarkers and their appropriate use in tests – another
336 important standardization task to improve data quality that is frequently underestimated [89].
337 Lessons learned from those studies allow iterative improvements of the therapeutic candidate or
338 patient selection by a back-to-bench-forward-to-bed approach ("refined translation") - an important
339 de-risking process [3,75].

> *"… despite the substantial resources invested into basic biomedical research, a vast majority of findings will never be tested in humans, let alone culminate in change in clinical practice."*
>
> R. Ogier, W. Knecht, and M.E. Schwab [94]

340

341 **5   Conclusions**

Literature points many fingers at causality in assessing challenges in the translational biomedical research enterprise [3–8,74,75,90–92]. Research waste, lost opportunities for impact, and inefficiency are natural products of collective failure across the biomedical research enterprise to enact long-recognized changes necessary to improve translational processes and clinical impact. Scientists and clinical researchers operate in a global theatre in which biomedical research is governed by incentives that oppose such changes, enforcing the status quo to the detriment of best translational practices, patient welfare and quality of life, stewardship of resources and societal support, and scientific credibility. A call for an improved "mind-set" and broader education of the next generation of biomedical and clinical researchers will in itself be insufficient to address data reproducibility, reporting, relevance and reliability challenges. Differences between academic and industrial missions, research strategies and conduct, and reward structures in biomedical research and translation must be appreciated and harmonized for translational congruence [93]. In some instances, a similar biomedical translational goal involving both academic and industry has resulted in surprisingly disparate intellectual property estates demonstrating orthogonal priorities and different translational strategies [94]. Stakeholder messaging and peer expectations for change provided to the translational research community must be consistent, persistent and focused. As global understanding of human disease mechanisms and markers broadens and improves, periodic revisiting and critically evaluating 'standard' biomedical research models, and their expected deliverables, are critical. We must continually review whether existing models – *in silico, in vitro, ex vivo, in vivo* - and the underlying data and hypotheses that drive them remain valid as new data emerge. Continual re-evaluation and critique of research approaches, models and data reporting will continue to inform, but should be better enforced on the research community by diverse stakeholders, to evolve best practices. Towards this end, seeking actual clinical validity of novel interventions and therapies will be more convincing than continually improving pre-clinical models attempting to duplicate clinical reality. But engaging in such practices must also be reinforced by the proper research incentives to more efficiently steer the investigating and translating community and more reliably assess and report their medical utility and clinical benefit [93].

High quality biomedical evidence across the diverse different biomedical sources – molecular/cellular, preclinical whole organism, computational in silico, case series, clinical trials, meta-analyses, patient-clinician engagement, and societal evidence (e.g., advocacy groups) – must be reliably selected and supported, collected, vetted and fairly reported to achieve best evidence-based medical care. Numerous known research deficiencies preclude realization of a reliable, efficient biomedical research system. Critically, stakeholders must show the resolve and initiative to properly incentivize the

376 research system to enable best practices systemically across the biomedical research spectrum. Only
377 with dedicated and persistent focus on holistically improving biomedical research process and
378 resulting data quality and reliability emanating from "bench to bedside and back" will global
379 biomedical translational efficiency and impact improve to benefit patient quality of life.
380

381

386

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Highlights:

- Healthcare technology innovation is expected from biomedical research translation
- Moving biomedical research discoveries to clinically reliable outcomes is difficult.
- Few academic claims are actually verified in human patients.
- Biomedical research models and data reliability are increasingly questioned.
- Biomedical research strategies must better address the actual human condition.