CLINICAL INVESTIGATION

Engaging patients for drug repurposing: mapping the patient engagement continuum

"...if patients can provide more insight into their expectations regarding disease and health management, drug repurposing programs can ... incorporate both conventional and personalized nonconventional treatments."

Drug repurposing involves finding new indications for existing drugs or potential drug candidates. Drugs or candidates include those in clinical development with relevance to multiple diseases, drugs that have failed to demonstrate efficacy for a particular indication during clinical trials but have no major safety concerns, discontinued drugs, drugs not yet fully pursued and drugs for which patents are set to expire [1]. Opportunities for drug repositioning can arise from indirect observation as well as purposeful collaboration including physician and patient engagement. The focus of this editorial is primarily on the engagement of patients directly or through patient information to support drug repurposing endeavors.

Engagement must permit the transition of patients from the role of simple participant to the mid-level informative role, and at the highest level of engagement the collaborative role.

Table 1 outlines a newly devised continuum of patient engagement. The focus is on the engagement of the 'lead patient' [2]. 'Lead patients' – namely those patients that: are proactive with respect to their health, disease and treatment options, can provide a nuanced perspective to drug discovery, including through repurposing endeavors [2]. Specifically, patients can be a source of direct information with respect to off-label drug usage, patient records and patient communities can indirectly reveal drug repurposing opportunities, and patients can jointly collaborate in the search for new drug repurposing opportunities through the deciphering of information on drug pharma-cology – system or – gene interaction or other design opportunities [3]. The engagement could not be more salient than for rare disease drug repurposing [4].

Engaging patients & leveraging patient information for drug repurposing

The chance exists to engage patients directly through crowd research and patient journey mapping as well as indirectly through patient health information to seek new opportunities for drug repurposing. Below are several case examples that shed light on programs that have been initiated by a variety of stakeholders including patients themselves to elucidate drugs that potentially are candidates for drug repurposing.

Citizen science: collaborating with patients for drug repurposing

Litterman et al. discuss that social network sites enable physicians and patients alike to crowdsource a diagnosis particularly in the case of rare diseases. Through increased connectivity, patients can engage one another as well as physicians as they attempt to identify the source of their symptoms and understand their recent diagnoses [5]. Litterman et al. equally consider the need to assimilate and disseminate the necessary information to patients, physicians and advocates to gain insights into new treatment options and to identify new drug repurposing opportunities (including molecules approved for human use e.g., pharmaceuticals, nutraceuticals and other products). For example, information on

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Table 1. A discovery and development continuum for patient engagement.			
Engagement model	Participative	Informative	Collaborative
Health promotion	Patients engage in self-discovery of health and wellness	Patients share their experiences with respect to health and wellness	Patients may engage in community based health and wellness initiatives
Treatment design	Patients seek information regarding disease management and treatment options	Patients may share their preferences with respect to treatment and disease management	Patients select meaningful end points
Drug discovery	Patients may seek information on research priorities of public and private stakeholders	Patients supply information regarding the needed prioritization of research questions	Patients may participate in the search for promising new indications through crowd science or lead patient workshops
Clinical trials	Patients seek information regarding clinical trial enrollment opportunities	Patients may share their preferences with respect to clinical trial protocol development and data collection	Patients may be engaged in clinical trial protocol design and personalized data collection
Disease management	Patients engage in self-discovery in patient driven communities	Patients share their experiences with treatments, symptoms and disease management	Patient outcome-related data – notably with regard to symptoms, the impact of disease on quality of life and improvements, can be used in collaboration with patients in evaluating the effectiveness of treatments

approved medicines or remedies in which the pharmacology could be related to a specific physiological system and/or gene could reveal new treatment options and/or new drug repurposing opportunities; of course, the knowledge should be readily understood by professionals and nonprofessionals [5].

Similarly, EspeRare is a nonprofit organization that engages patients through patient groups and other key stakeholders to uncover the potential of existing molecules to address severe therapeutic unmet needs in rare diseases [6]. While the goal is to enable the translational exploration, from preclinical to clinical stage of unexplored opportunities through partnerships with academia and the private sector, with patient groups providing access to patients for clinical and commercial development, the potential exists to engage patients earlier in the process. Suggestions for patient engagement include gathering information from patients regarding meaningful end points, disease experiences (patient reported outcomes) and expected treatment benefits. In this sense, the patient can transition from the position of research subject to information provider, advisor and ultimately to the highest level of engagement as coresearcher [7] .

Citizen science takes science out of traditional academic or industrial environments and into the population at large – tapping into the power of the crowd [8]. Transparency Life Sciences (TLS) uses Indication Finder™ – a survey-based crowdsourcing tool designed to identify new indications for existing drug candidates [9]. Participants are presented with background information followed by questions regarding development issues for specific compounds. Survey responses are aggregated, presented to the crowd for analysis in addition to discussion and then the resulting data curated by experts. Selected candidates have the potential of being developed using the TLS Protocol Builder™ – a crowdsourcing platform for designing clinical trials in partnership with researchers, physicians and patients [10]. Patients can and are engaged through this discovery and design process.

Patient off-label drug usage: following the patient journey toward drug repurposing

If we analyze the oncology domain, it is known that off-label drug prescribing is common. The National Comprehensive Cancer Network (NCCN) estimates off-label use of drugs or biologic therapies for cancer in the USA [11]. For example, 78 and 75% of patients with breast or lung cancer respectively received US FDA-approved drugs; noteworthy is that 68 and 95% of these drugs respectively were used for off-label indications not approved by the FDA [12]. Researchers suggest that tracking off-label use of drugs and indications would be useful for obtaining more information about particular risk–benefit ratios for specific indications [13].

The Repurposing Drugs in Oncology (ReDO) Project, for example, seeks to repurpose well-known and well-characterized noncancer drugs for new uses in oncology [14]. The researchers acknowledge that data made available as part of the ReDO project could provide clinicians treating late stage cancer patients with additional avenues to explore in an off-label, off-trial drug usage [14]. With studies alluding to the role of practicing clinicians in field discovery, certainly, clinicians alongside their patients appear to be underestimated sources of invaluable information [15]. By engaging these stakeholders through crowd research, codesign and patient communities, it is anticipated that stakeholders will have the opportunity to elucidate formal drug repurposing opportunities.

Scanning patient communities & electronic health records: patient health information providing clues to drug repurposing

Wicks *et al.* discuss that patients with serious diseases may experiment with drugs that may not have received FDA approval for the condition [16]. Online patient communities can provide an environment to track such drug usage and outcomes. Wicks *et al.* describe an analysis of data from the website PatientsLikeMe of patients with amyotrophic lateral sclerosis. These patients experimented with lithium carbonate treatment [16]. A consortium of physicians, scientists and experts has further formed ALSUntangled to investigate the use of self-experimentation, complementary and alternative medicine, as well as off-label drug usage [17]. Aside from observing and counteracting safety concerns associated with self-experimentation, the study of patient self-experimentation could reveal an off-label usage or treatment combination worth studying in a regulated drug repurposing program [16]. At the very least, such patient communities will provide a source of lead patients – those patients who are proactive and well-informed about their health and disease conditions – who can be engaged directly.

Xu *et al.* recently assessed the feasibility of using electronic health records (EHRs) and automated informatics methods to efficiently validate the recent the drug repurposing association of metformin with reduced cancer mortality [18]. Scanning records of some 32,000 cancer patients seen at Vanderbilt since the mid-1990s, the team specifically sought 5-year survival data with and without exposure to metformin – a first-line therapy for Type 2 diabetes for more than five decades [19]. EHR data indicated that the use of metformin was associated with decreased mortality after a cancer diagnosis when comparing diabetic and nondiabetic cancer patients not on metformin. Hence its suggestion for use as a chemotherapeutic [18]. Site-specific cancers showing decreased mortality with metformin included breast, colorectal, lung and prostate cancer [19]. Researchers at Stanford University have likewise extracted (from the Stanford Translational Research Integrated Data Environment [STRIDE] – a collection of data on more than 2 million patients treated in the Stanford health system) de-identified medication data and associated medical conditions, to generate a list of distinct uses for off-label drugs [20].
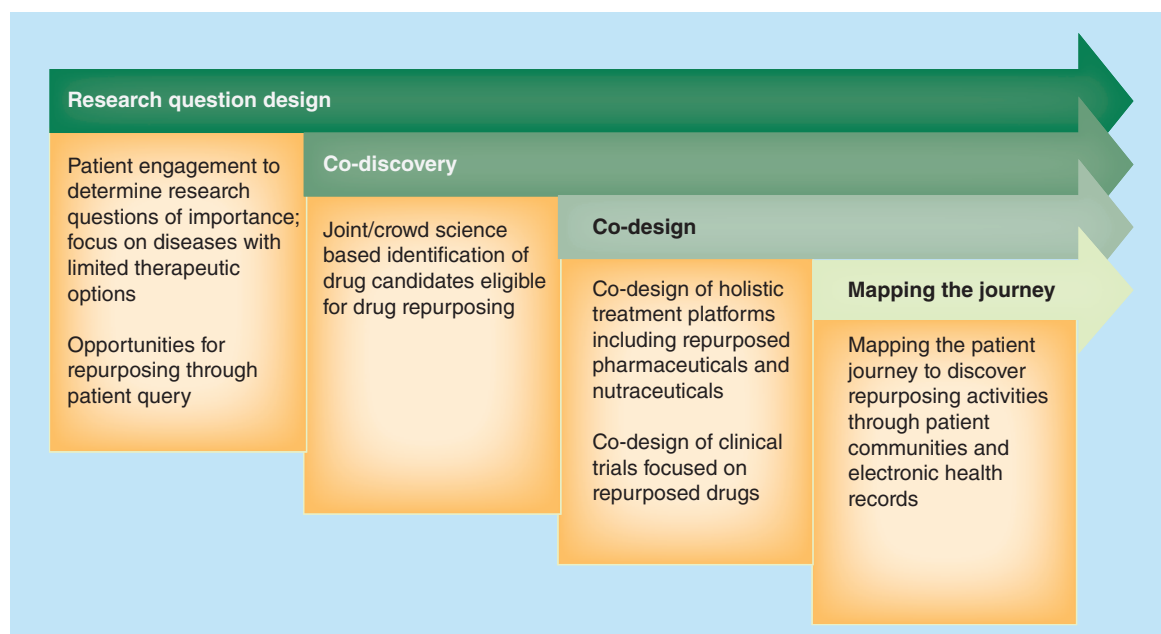
The drug repurposing engagement continuum

Although the traditional notion of value chain partner assumes engagement of the patient and patient advocacy groups during the later stages of drug development, lead patients should be sought to enable patient centric drug discovery and patient-centric clinical trial design. As patients themselves search for drug repurposing options, we can contend that joint engagement will offer the insight needed to design personalized, more holistic treatment platforms for end points and symptoms of value and for diseases with limited treatment options. Engagement strategies include direct, observational or analytical. We can envision with the prevalence of technological solutions to map the patient journey and permit patient access to electronic health records that patient engagement will move from the mid-informative level to the highest level of collaboration on the previously outlined continuum. Figure 1 represents the drug repurposing continuum suggesting engagement opportunities for patients during research question design, codiscovery of drug candidates, the design of treatment platforms including both repurposed pharmaceuticals and nutraceuticals, as well through patient journey mapping.

The challenge

There are however, several challenges ahead that stakeholders need to acknowledge namely: regulations surrounding patient engagement, privacy concerns particularly when engagement is indirect through electronic health records or patient communities, addressing the associated safety issues when patients independently repurpose drugs, and the extension of drug repurposing engagement to include nonconventional treatments such as nutraceuticals.

In this highly regulatory industry, stakeholders will need evolving guidelines on patient interaction. The differentiator here being patient engagement to understand product usage, treatment expectations, patient-driven repurposing. Of concern will be the protection of patient data – of paramount importance when collecting data from electronic health records or conducting data analysis on the basis of patient input via patient

Figure 1. The drug repurposing engagement continuum.

communities. Patient consent alongside transparency in either case are necessary to more openly engage patients. In parallel, open engagement will not only reveal patient or care giver driven off-label usage and/or experimentation, but guide such usage with regulated, scientifically driven data. Finally, the industry needs to increasingly acknowledge the role of nonconventional treatments in health and disease management. Critical is an understanding of the usage of such treatments by patients, impact on conventional medicine efficacy and potential drug repurposing opportunities. Bumb *et al.* recently discuss such opportunities in light of the failure of a number of new drugs for schizophrenia, suggesting repurposed compounds including nutraceuticals such as ω-3 fatty acids may serve as alternative and/or adjunctive agents for schizophrenic patients [21]. The sources from where repurposing opportunities may be sought must be broad particularly as we see the increased convergence between the pharmaceutical industry and the food and drinks industry. With patients willing to seek alternative solutions particularly where there is a lack of treatment

options, engagement earlier in the drug repurposing process can alleviate patient frustration, provide confidence in the regulatory drug discovery and development process and ensure that quality data can be collected from patients. Ultimately if patients can provide more insight into their expectations regarding disease and health management, drug repurposing programs can take an inclusive approach, that is, through the development of a holistic treatment platform – incorporating both conventional and personalized nonconventional treatments.

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