PHARMACOGENOMIC INVESTIGATION OF ADVERSE DRUG REACTIONS (ADRS): THE ADR PRIORITIZATION TOOL, APT

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ABSTRACT

Background
The impact of genetic factors on the risk of adverse drug reactions (ADRs) is being increasingly recognized as clinically important. ADR Prioritization Tool (APT) was developed to facilitate the prioritization of drugs and their associated ADRs for future pharmacogenomic studies.

Objectives
To describe a novel tool developed for the prioritization of pharmacogenomic investigation of ADRs and discuss the impact of specific scoring criteria.

Methods
APT scores were based on 25 key scientific and feasibility criteria relevant for clinical research evaluating the genetic basis of ADRs, with a maximum possible score of 60 points. The tool was independently applied to five ADRs (warfarin-induced bleeding/thrombosis, cisplatin-induced ototoxicity, methotrexate-induced neutropenia, carbamazepine-induced Stevens-Johnson syndrome, and abacavir-induced hypersensitivity) by two researchers. Scores were compared using the intraclass correlation coefficient (ICC) to determine level of agreement.

Results
Overall scores for target ADRs ranged from 19.5 to 44 points (33-73% of maximum possible score). Cisplatin-induced ototoxicity, a frequent and severe ADR, received the highest score (44). Lower scores were obtained for abacavir-induced hypersensitivity (19.5) and methotrexate-induced neutropenia (28). High agreement was observed between the scientific, feasibility, and total scores from two reviewers (ICC values = 0.895, 0.980, and 0.983, respectively).

Conclusion
Application of APT enables simple and direct comparison of potential study targets for research groups embarking on pharmacogenomic investigation of ADRs. Research teams will be able to identify which study targets are best suited for their research environment and discern how to optimize resource allocation for successful discovery and replication of clinically relevant biomarkers.

Key Words: *Pharmacogenomics, adverse drug reactions, ADR study prioritization*

Over a decade ago sequencing of the first human genome was completed, and with it came optimism and high expectations for personalizing medicine based on a patient's individual genetic make-up. It was anticipated that the identification of predictive genomic biomarkers of drug response would dramatically reduce the number of toxic responses to medications, possibly even eliminating a majority of adverse drug reactions (ADRs).[1] An increasing number of studies have demonstrated an important role for genetic variants in drug disposition and action pathways on the risk of adverse drug response.[2-8] However, ADRs remain a leading cause of morbidity and mortality, resulting in billions of healthcare dollars spent each year.[9,10] Most ADRs result from a mixture of clinical, environmental, and genetic factors, contributing to heterogeneity in response between individual patients taking the same drug, as well as differences in timing of ADR onset, severity, and clinical outcome among patients who experience the same reaction.[10] For many drugs, significant unexplained variability in toxicity remains even after accounting for clinical or demographic factors that can impact drug response.

With decreasing genotyping costs and advances in genome sequencing technology, the number of pharmacogenomic studies focusing on ADRs to address this unexplained variability continues to increase. Nevertheless, these studies remain an expensive undertaking. As the number of genetic variants that can be simultaneously tested increases, often so does the number of patients required to detect a true association and avoid false positive discoveries.[11] Similarly, as our understanding of the complexity of ADRs grows, there is an increasing awareness of the need for highly detailed characterization of patient-specific clinical events and outcomes, in order to capture relevant information that influences drug response. The substantial costs associated with recruitment and characterization of large cohorts of patients is a significant contributor to the cost of these studies.[12] There is a clear need for pharmacogenomic researchers to evaluate which ADRs are most likely to possess a genetic component that is feasible for investigation within their research setting.

The growing presence of national and international research networks and biobanks have provided additional opportunities for large-scale pharmacogenetic studies by facilitating patient recruitment and providing biospecimens for genetic analyses.[13] Such research networks also enable the study of a broad range of drugs and ADRs, making the prioritization of optimal study targets increasingly important. At the same time, the complex interplay of genetics and other factors influencing the risk of ADRs requires careful planning of studies to account for all possible confounding factors *a priori* and to select appropriate methods for genetic analyses.

Taken together, increasing opportunities for pharmacogenomic studies warrant careful consideration of the likelihood of genetic discovery, clinical relevance, and study feasibility in order to best utilize available resources. To assist pharmacogenomic researchers in addressing these fundamental issues, the objective of this study was to develop and review an ADR prioritization tool (APT) for comparing pharmacogenomic ADR study targets. APT addresses several key criteria that are relevant for determining which drugs and associated ADRs are best suited for study, including both scientific and feasibility criteria. Based on these criteria each ADR is awarded a priority score, with a higher score implying greater priority. The aim is to facilitate the selection of optimal study targets, as well as optimal study design with regards to type of genetic analyses, controlling for confounding factors, and planning of timelines and resource allocation. To highlight APT's content, five drug-ADR targets were selected and scored, and the overall scores and implications of specific criteria are discussed.

METHODS

The tool was comprised of two main sections: a scientific component and a feasibility component. In the scientific component, existing relevant knowledge on the drug and the ADR was considered, while the feasibility component addressed the practicality of undertaking a pharmacogenomic study within a given research setting based on logistics, finances, and expected

timeline. Both sections were given a maximum score of 30 points each, thus allowing a potential 60-point maximum score for each ADR target. The total score was based on 25 criteria chosen by expert consensus from researchers affiliated with the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). Each criterion was assigned a maximum and minimum score depending on the weight of that particular criterion to the overall score. In order to reduce the degree of variability in scoring among adjudicators, the scoring options for each criterion were clearly defined. In doing so, we attempted to achieve maximum comprehensibility and reproducibility of APT. The criteria details are displayed in Supplementary Tables S1-S5.

Scientific Component

The aim of this section was to capture existing scientific evidence from the literature regarding the use of the drug and its pharmacology, as well as the mechanism and impact of the ADR. Relevant information on four subsections were incorporated: Pharmacoepidemiologic and Pharmacotherapeutic Criteria, Economic Criteria, Genetic Criteria, and Biologic and Pharmacologic Criteria. The relative contributions (%) of each subsection to the scientific score are displayed in Figure 1 and were calculated as a percentage of the total score of 30 as displayed in Table 1.

FIG. 1 Relative weight of different criteria in the scientific and feasibility components (%)

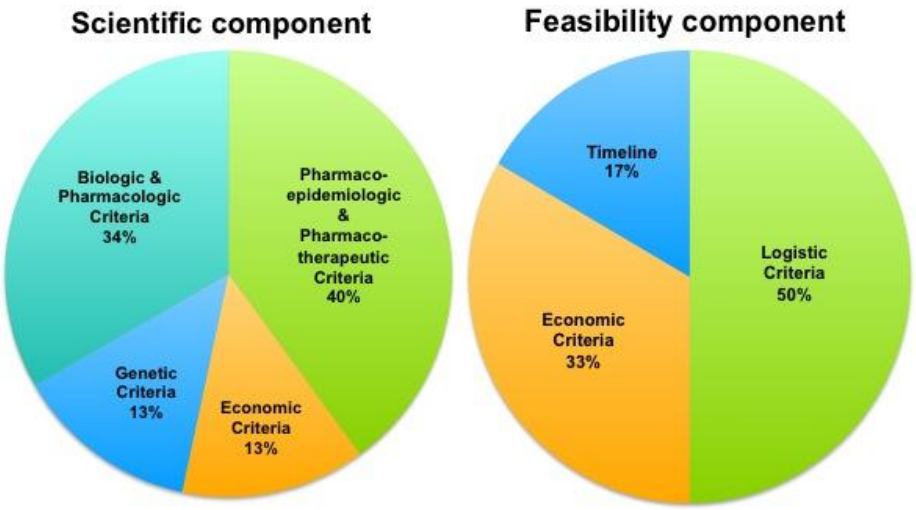


TABLE 1 Average criteria scores for five drug targets from two independent reviewers using prioritization algorithm

I. Scientific Component						
Item	**Score**	**Cisplatin Ototoxicity**	**Warfarin Bleeding/ Thrombosis**	**Methotrexate Neutropenia**	**Carbamazepine Stevens-Johnson Syndrome**	**Abacavir Hypersensitivity**
Pharmacoepidemiologic and Pharmacotherapeutic Criteria	**Max.score=12**					
P1. ADR is life-threatening or causes life-long disability	+ 3 (mandatory)	+3	+3	+3	+3	+3
P2. Reversibility of ADR	+ 1 to - 1	+1	0	-1	0	0
P3. Severity and burden of the ADR	+ 2 to 0	+2	+2	+0.5	+2	+2
P4. Monotherapy of combination therapy	+ 1 to - 1	-1	+0.5	-1	+1	-0.5
P5. Monitoring ADR progression	+ 1 to - 1	0	0	-1	+1	+1
P6. Number of patients that can be recruited	+ 2 to - 2	+1	+2	+1.5	+1.5	+1.5
P7. Percentage of patients expected to have the ADR	+ 1 to - 1	+1	+0.5	+1	-1	0
P8. Identification of control population	+ 1 to - 1	+0.5	+1.5	0	+1.5	+1.5
Economic Criteria	**Max.score=4**					
E1. Expectations for drug to remain on the market for 5 years	+ 2 to - 2	+2	+2	+2	+2	+2
E2. ADR treatment cost	+ 2 to - 2	+2	+2	0.5	+2	+2
Genetic Criteria	**Max.score=4**					
G1. Understanding of genetic component of the ADR	+2 to 0	+1	+2	+1	+2	+2
G2. Extent of unexplained phenotypic variation	+ 2 to - 2	+2	+2	+1.5	+2	+2
Biologic and Pharmacologic Criteria	**Max.score=10**					
B1. Understanding and complexity of drug metabolism	+ 1 to - 1	+1	+1	0	+1	+1
B2. Quantitative characterization of ADR	+ 3 to - 3	+3	+2.5	+3	0	+1
B3. Extent of overlap between ADR and disease	+ 1 to - 1	+1	0.5	+1	+1	+1
B4. Dose dependence of drug response	+ 1 to - 1	+1	+1	+1	-1	-1
B5. Understanding of ADR mechanism	+ 1 to - 1	0	+1	+1	-0.5	-0.5
B6. Ability of concomitant drug to cause ADR	+ 1 to - 1	0	+1	-1	0.5	+1
B7. Drug--drug PK or PD interaction	+ 1 to - 1	0	0.5	-0.5	0.5	+0.5
B8. Drug-disease PK or PD interaction	+ 1 to - 1	+0.5	0.5	+0.5	0.5	0
Total for the Scientific Component	**Max.score=30**	**21**	**25.5**	**13**	**19**	**19.5**
II. Feasibility Component						
Item	**Score**					
Feasibility for CPNDS Criteria	**Max.score=30**					
F1. Availability and accessibility of appropriate genotyping platform	+ 5 to - 5	+5	+5	+5	+5	+5
F2. Economic impact for research sustainability	+ 5 to - 5	+5	0	0	+5	+4
F3. Availability of pilot genotyping data	+ 5 to - 5	+3	+5	+3	+4	+4
F4. Extent of cohort collected and clinical characterization performed	+ 5 to - 5	+3	-5	+1.5	-3	-5
F5. Additional resources needed to approach the new target	+ 5 to - 5	+3	-1.5	+1.5	-1.5	-3
F6. Timeline to obtain meaningful results	+ 5 to - 5	+4	0	+4	-3	-5
Total for the Feasibility Component	**Max.score=30**	**23**	**3.5**	**15**	**6.5**	**0**
Grand Total	**Max.score=60**	**44**	**29**	**28**	**25.5**	**19.5**

1.1 PHARMACOEPIDEMIOLOGIC AND PHARMACOTHERAPEUTIC CRITERIA

P1: **ADR is life-threatening or causes life-long disability**

This first criterion was classified as mandatory and had a maximum value of 3 points, which was the highest number of points assigned to any individual criterion in the scientific component. We chose to mandate this criterion in our research setting to maximize therapeutic value of potential pharmacogenetic biomarkers in clinical care.

P2: **Reversibility of ADR**

A higher score was awarded to ADRs that result in irreversible damage (e.g. hearing loss, other permanent organ damage) given the associated long-term impact on quality of life and healthcare costs.

P3: **Severity and burden of the ADR**

ADRs that were considered severe or pose a high economic burden to the healthcare system were scored higher for this criterion. ADR severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.014.

P4: **Monotherapy or combination therapy**

A higher score was given to drugs that are used in monotherapy because of the reduced possibility of confounding factors, such as drug-drug interactions or similar ADRs caused by concomitant drugs, when analyzing associations between genetic variants and the ADR of interest.

P5: **Monitoring ADR progression**

ADR progression that can be easily monitored and prevented in clinical practice using a simple laboratory test received a lower score (e.g. monitoring methotrexate-induced neutropenia during chemotherapy using white blood cell counts). This is because a genetic test may not be necessary to prevent the ADR or to preclude its progression to a severe stage.

P6: **Number of patients taking the drug that can potentially be recruited per year**

Frequently prescribed drugs scored higher since a larger number of patients will be at risk for the ADR, increasing the clinical relevance of a pharmacogenetic test. Scoring details for patient numbers are displayed in Supplementary Table S1.

P7: **Percentage of patients expected to have the ADR based on estimated ADR incidence**

Similar to the previous criterion, a higher score was awarded to ADRs that are more frequent due to the increased number of patients at risk for the ADR and the associated increased clinical relevance and burden on the healthcare system.

P8: **Identification of control population**

A higher score was given to pharmacogenetic targets for which a large number of control patients with similar clinical covariates (e.g. age, gender, concomitant medications, etc.) compared to ADR cases can be identified. Matching cases to controls reduces the number of confounding factors in the analysis and increases statistical power to detect a genetic effect. Accordingly, a lower score was given to ADR targets that commonly cause a mild ADR, making the identification of true control patients a limiting factor and potentially resulting in false negative findings.

1.2 ECONOMIC CRITERIA

E1**: Expectations for drug to remain on the market for 5 years**

A higher score was awarded to drugs that are expected to remain in clinical use for at least another five years given the increased economic impact and long-term relevance of research findings. Scoring for this criterion was based on current or future availability of alternative therapies potentially replacing the drug, or indication that there is a high risk of serious adverse events that may lead to discontinuation of use of the drug in clinical practice.

E2: **Estimated impact and burden of the ADR in terms of cost to treat it**

Within this criterion, ADRs with a high cost of treatment (e.g. hospitalization, long-term follow-up costs) were given a greater priority score.

1.3 GENETIC CRITERIA

G1: **Understanding of genetic component of the ADR**

ADRs with strong evidence in the literature suggesting a genetic component received a higher priority score, as this increases the likelihood of the

discovery of clinically relevant pharmacogenomic markers. While such evidence can be based on previous pharmacogenetic studies, any evidence of a genetic basis, including heritability studies or familial occurrences, was also scored.

G2: **Extent of unexplained phenotypic variation between cases and controls**

ADRs with high phenotypic variation between cases and controls that cannot be explained by currently known clinical factors (e.g. concomitant drugs) were awarded a higher score as this increases the likelihood of a genetic basis. In addition, such high phenotypic variation allows researchers to select extreme phenotypes for a case-control study, which increases the power to detect genetic effects.

1.4 BIOLOGIC AND PHARMACOLOGIC CRITERIA

B1: **Understanding and complexity of drug metabolism**

A high score was awarded to drugs with a simple and well-defined metabolic pathway. Firstly, the likelihood of discovery of a single or small number of genetic variants of large effect is increased for a drug that is metabolized through a single, simple pathway. Secondly, knowledge of how the drug is metabolized and the relative importance of individual enzymes enable a more targeted investigation of specific genes, resulting in an increased power to detect a genetic association due to a decreased number of genetic variants studied.

B2: **Quantitative characterization of ADR**

This criterion addressed how well an ADR can be characterized based on clinical information. ADRs that can be measured and graded according to their severity using quantitative data were awarded a maximum score of 3, whereas ADRs that can only be assessed using qualitative data or have a highly variable clinical presentation were awarded a lower score. This criterion was given the highest possible number of points among all criteria in the scientific component.

B3: **Extent of overlap between ADR and disease for which the drug is taken**

ADRs with symptoms that can also be caused by the patient's underlying medical condition received a lower score for this criterion, as it is more difficult to distinguish true cases from controls when disease and ADR symptoms are overlapping.

B4: **Dose dependence of drug response**

ADRs for which ADR-risk is correlated with drug dosage received a higher score. In dose-dependent ADRs, unexplained variability (e.g. patients who develop the reaction at a low dose) is potentially related to genetic variation in drug absorption, distribution, metabolism, and excretion (ADME), making a targeted investigation of genes involved in drug ADME a favorable approach for a well-powered genetic study. ADRs that are dose-independent are more likely to require an exploratory study approach and are thus more likely to require larger sample sizes.

B5: **Understanding of ADR mechanism**

Similar to criterion B4, an understanding of the ADR mechanism allows for a more targeted study approach, which increases the probability of discovering genetic variants associated with the ADR.

B6: **Ability of concomitant drug to cause the ADR**

ADRs that can also be caused by a concomitant drug received a low score for this criterion, as it can be difficult to ascertain the causative drug for the ADR.

B7: **Drug-drug pharmacokinetic (PK) or pharmacodynamic (PD) interaction**

In addition to B6, concomitant drugs can also affect the PK or PD of the drug of interest (e.g. by inhibiting or inducing drug metabolizing enzymes). ADRs that are influenced by such drug-drug interactions received a lower score since the concomitant drug can act as a confounder in the analysis.

B8: **Drug-disease PK or PD interaction**

This criterion assessed the possibility for a patient's medical condition to act as a confounder by affecting the PK or PD of a drug. For example, induction of CYP2D6 during pregnancy can either increase or decrease the amount of active drug metabolite depending on the drug of interest[15]. As with the other similar criteria, the existence of such a confounding factor decreased the overall score of a drug.

2.0 FEASIBILITY COMPONENT

The second component of APT was the feasibility component, which addressed six criteria specific to a given research environment. This section was worth the same number of points as the scientific component (30 points), with each criterion ranging from -5 to +5. The six criteria were further subdivided into timeline (F6), economic criteria (F2 & F5), and logistic criteria (F1, F3 & F4) (Figure 1).

F1: **Availability and accessibility of appropriate genotyping platform**

Availability of the appropriate genotyping platform from either the host lab or a collaborative lab increased the feasibility score as this can reduce the amount of funding required for new equipment and shorten the study timeline. Depending on how much is already known about the ADR mechanism, drug ADME, or the genetic basis of the ADR, the appropriate genotyping method may vary between different pharmacogenomic targets. All genotyping platforms can receive maximum points, as the goal of this criterion was to evaluate the availability of the platform and not the choice of platform itself.

F2: **Economic impact for research sustainability**

Studies expected to produce novel and clinically relevant results have a greater potential to be published in high impact journals, attract research funding, or lay the foundation for a new genetic test. All of these factors could directly or indirectly generate revenue to ensure the sustainability of a research group. In order to gain maximum points for this criterion, an ADR must be clinically relevant with the genetic associations also being poorly understood. If genetic variants associated with an ADR have already been discovered and validated, this can limit the potential for new discovery and thus the potential for revenue to fund future research.

F3: **Availability of pilot genotyping data**

Within this criterion, ADRs with significant pilot data available (e.g. previous pharmacogenetic studies performed in other patient populations, in-house pilot data) received additional points. Knowledge gained from previous studies investigating the same ADR would increase the feasibility of a study by increasing the chance of a positive finding and reducing the number of genes to analyze.

F4: **Extent of patient cohort collected and clinical characterization performed**

Obtaining a sufficient number of well-characterized cases and controls is vital for a pharmacogenetic study in order to obtain sufficient statistical power to detect genetic effects. Accordingly, having a clinical cohort already collected but not adequately characterized can limit study feasibility, as clinical characterization is often a complicated and time-consuming process and can substantially impact the study timeline.

F5: **Additional resources needed to approach the new target**

The scoring for this criterion assessed the availability of funding and the amount of resources required to conduct a study (e.g. amount of time and personnel needed to obtain samples and perform clinical characterization, cost of genotyping, additional equipment required, bioinformatics costs, etc.). Studies for which sufficient funding has already been obtained, or which have progressed to the point that no additional resources are required, will have the greatest probability of being completed and were awarded the highest score.

F6: **Timeline to obtain meaningful results**

A shorter timeline increases the likelihood of completion of a study, the novelty and relevance of results, and reduces the additional resources required. An anticipated timeline of less than 6 months earned maximum points for this criterion.

Application and Assessment of Inter-rater Reliability

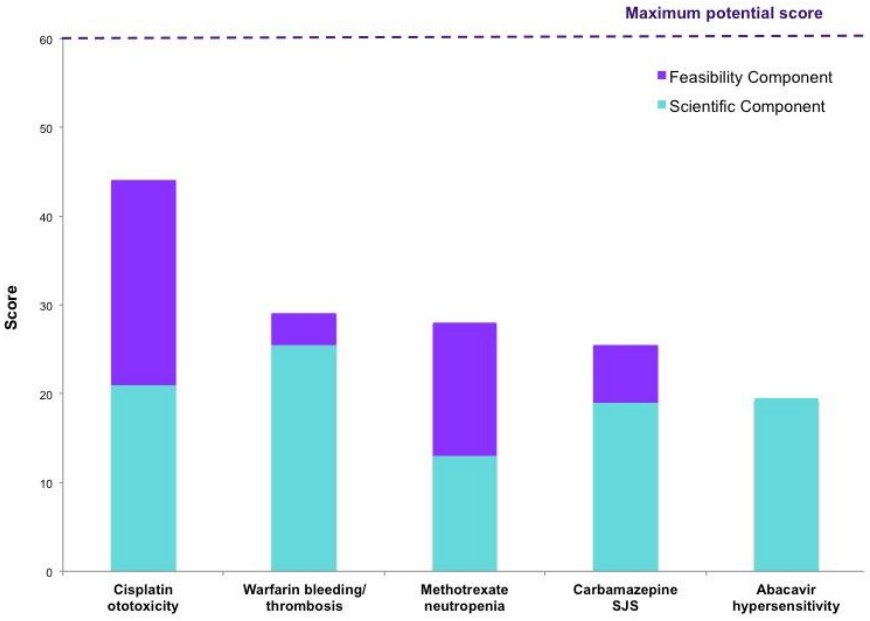
APT was independently applied to five drug-ADR targets by two researchers from CPNDS[16]. The five targets chosen were: warfarin-induced bleeding and thrombosis, carbamazepine-induced Stevens-Johnson syndrome (SJS), methotrexate-induced neutropenia, cisplatin-induced ototoxicity, and abacavir-induced hypersensitivity. These targets were purposely chosen for comparison in order to highlight the impact of specific APT criteria on overall scores.

Scores in the scientific component were based on information available in the literature while scores in the feasibility component were assessed specifically to the research environment within CPNDS, which has predominantly focused on ADRs in pediatric oncology patients. The scores from both reviewers for each criterion were averaged and component scores, as well as the total scores from both reviewers were compared using the intraclass correlation coefficient (statistical software R, irr package).[17,18]

RESULTS

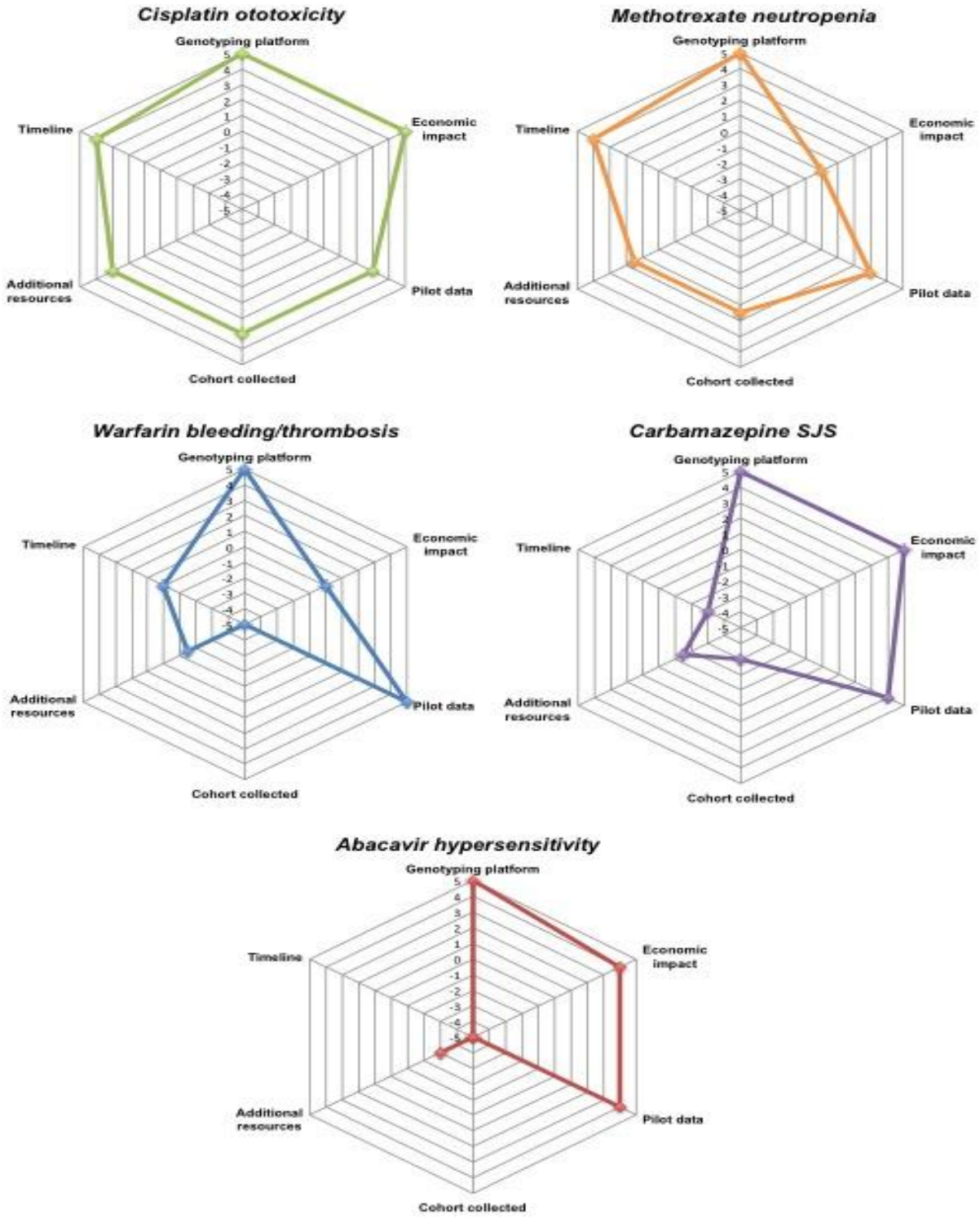
Cisplatin-induced ototoxicity obtained the highest priority rating with a score of 44 points, followed by warfarin-induced bleeding/thrombosis (29 points), methotrexate-induced neutropenia (28 points), carbamazepine-induced SJS (25.5 points), and abacavir-induced hypersensitivity with the lowest score of 19.5 points (Figure 2). The total scores ranged from 33% (19.5/60) to 73% (44/60) of the maximum possible score. The scoring details for each target are displayed in Table 1. Of all ADR targets, warfarin-induced bleeding/thrombosis scored the highest for the scientific component while methotrexate-induced neutropenia scored the lowest. For the feasibility component, cisplatin-induced ototoxicity received the highest score and abacavir-induced hypersensitivity ranked last. The scores for the scientific component were relatively similar across ADR targets, ranging from 13 to 25.5 points, whereas the variability in scoring for the feasibility component was much higher, ranging from 0 to 23 points. The scoring of the feasibility component thus primarily influenced major differences in total scores between ADR targets. Radar charts illustrating the feasibility scores for each target are displayed in Figure 3. The detailed scoring for each ADR target is described below.

FIG. 2 Component scores and total scores for five ADR targets as determined by two independent reviewers



	Cisplatin ototoxicity	Warfarin bleeding/ thrombosis	Methotrexate neutropenia	Carbamazepine SJS	Abacavir hypersensitivity
Scientific Score	21	25.5	13	19	19.5
Feasibility Score	23	3.5	15	6.5	0
Total Score	**44**	**29**	**28**	**25.5**	**19.5**

FIG. 3 Radar charts illustrating feasibility criteria scores (from highest to lowest) for five ADR targets



Cisplatin-induced Ototoxicity

Cisplatin-induced ototoxicity was the only ADR target that received greater than 20 points for both components, resulting in the highest overall score (Figure 2). This ranking was mainly due to high scores for scientific criteria addressing the severity and burden of the ADR, existing knowledge of a genetic basis, quantitative detection of the ADR, as well as a lack of confounding factors (Table 1). In the feasibility component, cisplatin-induced ototoxicity received the highest score of all ADR targets. This can be attributed to maximum scores for availability of the appropriate genotyping platform, high economic impact, and a relatively short timeline to obtain results (Table 1; Figure 3).

Warfarin-induced Bleeding/thrombosis

Warfarin obtained the highest score in the scientific component (Table 1; Figure 2). This result is not surprising as the metabolism, mechanism of action and pharmacogenetics of warfarin have been extensively characterized in the literature. The large number of patients prescribed warfarin and the high ADR frequency also made warfarin a favorable target from a pharmacoepidemiologic standpoint. On the other hand, warfarin received a relatively low score in the feasibility component, mainly due to a lack of cohort already collected and the associated impact on additional resources and time required to obtain results (Table 1; Figure 3). Furthermore, a low score was given for the economic potential for research sustainability due to already well-established pharmacogenetic markers.

Methotrexate-induced Neutropenia

Methotrexate-induced neutropenia received the lowest score for the scientific component, in spite of existing knowledge on the ADR mechanism, drug metabolism, high ADR frequency, and quantitative detection. This low score was mainly attributable to the reversibility of the ADR, as well as the reduced severity and lower cost of treating the ADR (e.g. delaying chemotherapy) compared to other ADRs scored (Table 1). Furthermore, negative scores were obtained for possible confounding factors, such as concomitant medications causing the same ADR and the primary use of methotrexate in a combination therapy. Methotrexate-induced neutropenia was also the only target that received a negative score for "monitoring ADR progression" (criteria P5) due to the possibility of measuring white blood cell count and neutropenia progression with a simple blood test (Table 1). Regarding the feasibility component, methotrexate-induced neutropenia received the second-highest score of all ADR targets, mainly due to availability of an appropriate genotyping platform and a short timeline based on frequent use, high ADR incidence and a partially collected clinical cohort (Table 1; Figure 3). On the other hand, the lack of pilot data and a relatively low interest in clinical genotyping had a negative impact on the feasibility score.

Carabamazepine-induced SJS

Carbamazepine-induced SJS scored fairly low in both components (Figure 2). For the scientific component, the main criteria that impacted the score were the extreme rarity and dose-independence of the ADR, as well as limited knowledge of the ADR mechanism. The lack of a quantitative test for SJS and the associated difficulties in differentiating SJS from other carbamazepine-induced hypersensitivity reactions further contributed to the low score (Table 1). Conversely, a high score was obtained for severity and burden of the ADR and previous knowledge of a genetic basis. The rarity of carbamazepine-induced SJS also had a strong impact on the feasibility score, resulting in low scores for number of patients already recruited, additional resources required and anticipated timeline (Table 1; Figure 3). However, the unpredictability and severity of the ADR suggests that there should be high interest in clinical genotyping for predictive genetic variants.

Abacavir-induced Hypersensitivity

Abacavir-induced hypersensitivity scored very similarly to carbamazepine-induced SJS, with the feasibility score also being greatly impacted by the rarity of the ADR (Table 1). In contrast to carbamazepine, the limited number of patients prescribed abacavir in our primary study population (pediatric patients) resulted in negative scores for cohort collected and timeline to obtain

results (Table 1; Figure 3). Abacavir-induced scientific component for many of the same reasons as SJS, such as dose independence, unknown mechanism, and potential drug-drug and drug-disease interactions (Table 1). However, abacavir-induced hypersensitivity occurs more frequently than SJS and can potentially be characterized using laboratory tests, such as skin patch testing, resulting in a higher scientific score.

Inter-rater Reliability

To determine the reproducibility of APT, scores from both raters were compared using the intraclass correlation coefficient (ICC). Good agreement was observed for both the scientific and feasibility components scores, as well as for the total scores. When applying a two-way agreement model, which took into account absolute differences in scores, the ICC scores for the scientific component, feasibility component, and overall scores were 0.90 (CI:0.30-0.99), 0.98 (CI:0.471-1.0), and 0.98 (CI:0.79-1.0), respectively (Table 2). A consistency model, which evaluated relative scores of ADR targets between raters, also produced similar ICC values (0.88, 0.99, and 0.99) (Table 2).

TABLE 2 Inter-relater reliability: intraclass correlation coefficients (ICCs)

	Type of ICC Model	
	Two-way Agreement Model ICC Values	**Two-way Consistency Model ICC Values**
Scientific Component Scores	**0.90** (0.30-0.99)	**0.88** (0.23-0.99)
Feasibility Component Scores	**0.98** (0.47-1.0)	**0.99** (0.93-1.0)
Total Scores	**0.98** (0.79-1.0)	**0.99** (0.91-1.00)

DISCUSSION

More than a decade after the sequence of the human genome was revealed, prescribing an appropriate therapy for an individual patient still relies predominantly on empiric and trial-and-error decision-making, contributing to a consistently high incidence of ADRs worldwide. With current trends in decreasing genotyping costs and enhanced sequencing technology, the potential for discovery and use of predictive drug-response variants is becoming increasingly feasible. Even so, pharmacogenomic researchers must prioritize ADR targets for investigation in order to optimize efficient research and increase the likelihood of clinically relevant results.

We developed a prioritization tool that highlights key elements for comparative

evaluation of pharmacogenomic study targets and demonstrated its performance by completing a detailed comparison of ADRs. The intent was not to provide a validation of the tool but rather to discuss the impact of specific ADR characteristics on APT scores using well-known pharmacogenomics examples.

To assess the performance of this novel tool we purposely chose five ADR targets for comparison that were expected to differ in many aspects. Warfarin-induced bleeding/thrombosis was evaluated in order to assess the performance of APT for a target where a high priority score was expected, given the high frequency of the ADR and previously established pharmacogenetic markers. Conversely, carbamazepine-induced SJS and abacavir-induced hypersensitivity are both rare reactions that were intended to highlight the effect of low ADR frequency on feasibility scores, while cisplatin-induced ototoxicity was expected to score well in the feasibility component due to CPNDS's current focus on ADRs in oncology patients and ongoing research in cisplatin-induced ototoxicity in children.[3] Our observation of results that were similar to those expected suggests that the criteria chosen for APT and the weight awarded to each criterion provide the intended assessment of potential targets.

In the scientific component, a heavy emphasis was given to ADR severity. This was reflected by a high scientific score for SJS, which is severe and life threatening, compared to a low scientific score for neutropenia, which most often presents as a mild ADR that can be monitored to avoid progression to a severe stage. While mild ADRs can present a significant burden by causing drug discontinuation and subsequent prolongation of therapies, the intent was to avoid deprioritizing rare but clinically relevant ADRs. Rather, APT enables the identification of challenges associated with studying less common ADRs, such as long timelines and small patient cohorts, so that these challenges can be planned for *a priori*.

In contrast to the scientific component, the feasibility component was designed to be specific to a given research environment, as highlighted by the scoring for cisplatin-induced ototoxicity. Since completion of the original CPNDS genetic association study, additional cisplatin patients have been recruited for the purposes of replication and validation studies. As a result, cisplatin-induced ototoxicity received the highest feasibility score due to the associated reduction in time and resources required for a replication study. On the other hand, warfarin-induced bleeding/thrombosis obtained a low feasibility score in spite of a favorable scientific score due to the pediatric focus of the research environment for which scoring was performed and the infrequent use of warfarin in children.

Even though both components were given equal weight, the feasibility component had a larger influence on the variation in total scores between targets. This was partly due to the smaller number of criteria listed in the feasibility component, as well as the larger range of points allotted for each criterion. Nevertheless, the strong weight on study feasibility was intended in order to avoid inappropriate resource allocation to studies that are not optimally feasible within a given research environment.

The two components also provide different, yet useful information regarding potential study design for specific ADR targets. In general, ADR targets scored higher in the scientific component compared to the feasibility component, implying that while some targets are extensively characterized and have a known genetic component, a study may not be feasible based on the number of patients already collected or additional time and resources required to obtain results. Collaborations with other research groups or further access to patients taking the drug of interest are just two factors that could substantially change the feasibility score, especially for rare ADRs. Awareness of factors that are likely to impact study feasibility allows researchers to devise a plan that will address these challenges prior to study initiation. In contrast, the scientific component can assist with deciding what type of genetic study is optimally suited for an ADR target. For example, the scientific score can reveal that the ADR mechanism or drug metabolism pathways are not well characterized, indicating that a broader and more exploratory genetic approach may be most appropriate.

Additionally, the scientific component enables the identification of potential confounders

before study initiation to ensure that they can be accounted for at all stages of the study.

It is vital to emphasize that the key focus of APT should not be on the absolute scores of most valuable information. The majority of ADR targets did not receive a score greater than 50% of the potential maximum score. Therefore, we did not aim to determine a threshold above which a target would be deemed a good study candidate. Similarly, the scientific and feasibility components scores should also be compared separately and relative to each other in order to gain the maximum amount of information. For example, warfarin-induced bleeding/thrombosis and methotrexate-induced neutropenia scored very similarly overall (29 points vs. 28 points); however, when examining the scores more closely, warfarin performed well in the scientific component while methotrexate scored higher in the feasibility component. This suggests that while both targets appear to be on par in terms of priority, the proposed studies would be vastly different with respect to recruitment, phenotyping, genotyping strategy, and timeline. This demonstrates how comparing component scores separately allows researchers to choose a target that better suits their desired study design and research goals within their own research setting. APT was not designed to be a final decision-maker when selecting ADR targets for investigation. The high ICC values obtained demonstrate the reproducibility of scores between raters based on the detailed descriptions provided for each criterion. However, the overarching goal was to develop a tool that would highlight the multitude of factors that need to be considered before approaching a pharmacogenomic study. Overlooking or ignoring important factors or confounders can lead to early termination of studies, overuse of resources, inappropriate resource allocation or false-positive results. APT enables researchers to compare strengths and weaknesses of ADR targets and to assist in improved study design by identifying potential confounders or pitfalls. It will thus facilitate the planning of future pharmacogenetic studies, ultimately leading to successful outcomes and advances in the field of pharmacogenomic research.

ADR targets. Rather, it is the ranking of ADR targets relative to each other that provides the

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Supplemental Table S1
Details of the pharmacoepidemiologic and pharmacotherapeutic criteria of the target drug prioritization tool

I. Scientific Component				
Code	**No.**	**Item**		**Score**
Pharmacoepidemiologic and Pharmacotherapeutic Criteria				**Max. score = 12**
P	1	ADR is life-threatening or causes life-long disability		+ 3 (mandatory)
P	2	ADR reversible (with dose reduction or discontinuation) or irreversible		+ 1 to - 1
		-1	Reversible ADR	
		0	Unknown or partial reversibility only	
		+1	Irreversible ADR	
P	3	Estimated severity and burden of the ADR		+ 2 to 0
		0	Moderate ADR (according to CTCAE criteria) and burden	
		+1	Severe ADR (according to CTCAE criteria) and high burden	
		+2	Life-threatening ADR (according to CTCAE criteria) and very high burden	
P	4	Monotherapy or combination therapy		+ 1 to – 1
		-1	Drug is primarily used as part of combination therapy	
		0	Drug is sometimes used as monotherapy	
		+1	Drug is primarily used as monotherapy	
P	5	Monitoring ADR progression		+ 1 to – 1
		-1	ADR progression can easily be monitored (e.g. using a simple inexpensive test)	
		0	ADR progression can be monitored using a complex (e.g. costly, labor-intensive, time-consuming) method	
		+1	ADR progression cannot be monitored	
P	6	Number of patients taking drug that can be potentially recruited per year		+ 2 to – 2
		-2	Very low number of patients (<100 patients/year)	
		-1	Low number of patients (100-200 patients/year)	
		0	Moderate number of patients (200-500 patients/year)	
		+1	High number of patients (500-1,000 patients/year)	
		+2	Very high number of patients (>1,000 patients/year)	
P	7	Number of patients expected to have ADR based on estimated ADR incidence		+ 1 to – 1
		-1	Low number experiencing ADR ($\leq$1%)	
		0	Moderate number experiencing ADR (2-9%)	
		+1	Large number of patients experiencing ADR ($\geq$10%)	
P	8	Control population identifiable		+ 1 to – 1
		-1	Small identifiable matched control population (<1:2 case-control ratio)	
		0	Moderate size identifiable matched control population	
		+1	Large identifiable matched control population (≥1:4 case-control ratio)	

Supplemental Table S2
Details of the economic criteria of the target drug prioritization tool

I. Scientific Component (continued)				
Code	**No.**	**Item**		**Score**
Economic Criteria				**Max. score = 4**
E	1	Expected to remain on the market for 5 years		+ 2 to - 2
		-2	Expected to remain on the market for less than 5 years	
		0	Expected to remain on the market for approximately 5 years	
		+2	Expected to remain on the market for more than 5 years	
E	2	Estimated cost burden of ADR treatment		+ 2 to 0
		0	Moderate cost burden of treating ADR	
		+1	High cost burden of treating ADR	
		+2	Very high cost burden of treating ADR	

Supplemental Table S3
Details of the genetic criteria of the target drug prioritization tool

I. Scientific Component (continued)				
Code	**No.**	**Item**		**Score**
Genetic Criteria				**Max. score = 4**
G	1	Known genetic component of ADR		+ 2 to - 2
		-2	Unknown genetic component associated with ADR	
		-1	Weakly associated genetic component linked to ADR	
		0	Potential genetic component associated with ADR	
		+1	Established genetic component associated with ADR	
		+2	Strongly-established genetic component associated with ADR	
G	2	Extent of unexplained phenotypic variation between cases and controls		+ 2 to – 2
		-2	Very low phenotypic variation	
		-1	Low phenotypic variation	
		0	Moderate phenotypic variation	
		+1	High phenotypic variation	
		+2	Very high phenotypic variation	

Supplemental Table S4
Details of the biologic and pharmacologic criteria of the target drug prioritization tool

I. Scientific Component (continued)				
Code	**No.**	**Item**		**Score**
Biologic and Pharmacologic Criteria				**Max. score = 10**
B	1	Simple vs. complex drug metabolism		+ 1 to - 1
		-1	Unclear/unknown pathway of drug metabolism	
		0	Complex but clearly defined pathway of drug metabolism (e.g. multiple pathways), or partially known pathway of drug metabolism	
		+1	Known, simple pathway of drug metabolism (e.g. single pathway)	
B	2	Clinical characterization of ADR		+ 3 to - 3
		-3	Weak qualitative detection of ADR	
		-2	Moderate qualitative detection of ADR	
		-1	Strong qualitative detection of ADR	
		0	Weak quantitative detection of ADR	
		+1	Moderate quantitative detection of ADR	
		+2	Strong quantitative detection of ADR	
		+3	Very strong quantitative detection of ADR	
B	3	Overlap between ADR and disease for which the drug is taken		+ 1 to - 1
		-1	ADR signs and symptoms can also occur from underlying disease	
		0	Potential overlap between ADR and disease	
		+1	No overlap between ADR and disease	
B	4	Dose-dependent ADR		+ 1 to - 1
		-1	ADR occurs independent of drug dose	
		0	Unknown if ADR is dose-dependent	
		+1	ADR is dose-dependent	
B	5	Exact mechanism of ADR is clearly understood		+ 1 to - 1
		-1	Unknown mechanism of ADR	
		0	Postulated only mechanism of ADR	
		+1	ADR mechanism is clearly understood	
B	6	ADR can be caused by a concomitant drug[1]		+ 1 to - 1
		-1	ADR can be caused by concomitant drug	
		0	Unknown if ADR could be caused by concomitant drug	
		+1	ADR is not caused by concomitant drug	
B	7	ADR can be caused by a drug-drug PK or PD interaction		+ 1 to - 1
		-1	ADR can be caused by a drug interaction	
		0	Unknown if ADR is caused by a drug interaction	
		+1	ADR is not caused by a drug interaction	
B	8	ADR can be caused by a drug-disease PK or PD interaction		+ 1 to - 1
		-1	ADR can be caused by a drug-disease interaction	
		0	Unknown if ADR is caused by a drug-disease interaction	
		+1	ADR is not caused by a drug-disease interaction	

Supplemental Table S5
Details of the feasibility criteria of the target drug prioritization tool

II. Feasibility Component				
Code	**No.**	**Item**		**Score**
Feasibility for CPNDS Criteria				**Max. score = 30**
F	1	Appropriate genotyping platform available and accessible		+ 5 to - 5
		-5	Genotyping platform is not available or accessible	
		-3	Genotyping platform is available with limited access	
		+3	Genotyping platform is available with moderate access	
		+5	Genotyping platform is available with full access	
F	2	Economic impact for research sustainability		+ 5 to - 5
		-5	Very low potential for new discovery with no interest in clinical genotyping	
		-3	Low potential for new discovery with low or moderate interest in clinical genotyping,	
		0	Moderate or high potential for new discovery with low interest in clinical genotyping; or low potential for new discovery with high interest in clinical genotyping	
		+3	Moderate potential for new discovery with moderate or high interest in clinical genotyping	
		+5	High potential for new discovery with high interest in clinical genotyping	
F	3	Pilot genotyping data already available		+ 5 to – 5
		-5	Pilot studies negative for all examined variants	
		-3	No pilot studies available	
		+3	Candidate variants identified but lacking patient numbers for sufficient statistical power	
		+5	Highly associated candidate variants identified	
F	4	Cohort of patients already collected and clinical characterization performed		+ 5 to – 5
		-5	Cohort not collected	
		-3	Only small cohort collected, significant additional patient recruitment and clinical characterization required	
		0	Clinical cohort partly collected, additional patient recruitment and clinical characterization required	
		+3	Majority of clinical cohort already collected but limited clinical characterization performed	
		+5	Cohort already collected and clinical characterization completed	
F	5	Additional resources needed to approach the new target (e.g. for patient recruitment, genotyping, clinical characterization, etc.)		+ 5 to - 5
		-5	Extensive additional resources needed	
		-3	Significant additional resources needed	
		0	Some additional resources needed	
		+3	Few additional resources needed	
		+5	No additional resources needed	
F	6	Timeline to obtain meaningful results		+ 5 to - 5
		-5	Very long timeline (>24 months) to obtain meaningful results	
		-3	Long timeline (18-24 months) to obtain meaningful results	
		0	Moderate timeline (12-18 months) to obtain meaningful results	
		+3	Short timeline (6-12 months) to obtain meaningful results	
		+5	Very short timeline (3-6 months) to obtain meaningful results	