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FinnGen: combining genetics, medical phenotype and population registry data to advance drug discovery

Why Finland, why now?

Human genetics has matured to a point where the assessment of genotype-phenotype relationships in large populations can inform drug discovery efforts by identifying novel targets, informing on potential target safety and through establishing biomarkers that could serve as surrogate endpoints. With years of longitudinal data and medical phenotypes from across the clinical spectrum, such population medical resources offer deeper opportunities to understand patient heterogeneity, therapeutic response, and unexpected potential connections between disease and therapy. **Finland offers three major advantages for genetic discovery and population follow-up not found together in any other country:**

(i) **centralized, Nordic medical record and registry system fully available to research**: Medical, prescription and many other national registries have been centrally collected for decades and are available to research. Thus, lifelong medical histories, including hospitalizations and outpatient diagnoses, prescription medications with diagnoses and use of social services, can be used to create unique longitudinal phenotypes. Of note, significant investments in epidemiology in the 1980's and '90's created large data sets of individuals with extensive phenotype data as well as blood and other biospecimens collected decades ago, with now several decades of incident medical data recovered from

(ii) **Unique biobanking legislation:** Furthermore, a Biobank Law was approved by the Finnish Parliament in 2012 and took effect in 2013 establishing a national biobank. Among key features is that the law permits recontacting of study subjects (by genotype or phenotype) for follow-up phenotyping across all domains of biomedicine, and provided a mechanism by which samples collected in the past (such as the valuable epidemiology cohorts), as well as those consented now, could be moved to the national biobank. Importantly, the law enables the biobank to be constructed in a fashion that allows use of all samples in future research not specifically explained to each consenting participant. The FinnGen project is being conducted entirely through this national biobank system.

(iii) **Unique population genetic history**: A strong founding bottleneck ~120 generations ago causes some strongly deleterious alleles to be considerably more common than expected, greatly facilitating the identification of specific genotype-phenotype connections in medical genetics research. This same bottleneck also simplifies the allelic spectrum meaning that these deleterious alleles are seen in many individuals in the population (offering advantages for recall studies) rather than the diverse set of ultra-rare variants, intermingled with neutral ones, found in most populations. Finally, it is well established that imputation-based reconstruction of whole-genomes works substantially better in founder populations, suggesting we can more easily and inexpensively reach down to very rare frequencies via such methods.

With the unique research opportunities derivable from these advantages, we initiated the FinnGen project to construct an academic-pharma partnership to develop the potential of these resources to serve medicine – in practice in Finland, and via improving the efficiency and safety of drug

development, worldwide. The project was launched in August 2017 with roughly 2/3 of the funding from 7 pharmaceutical partners (Abbvie, Astra-Zeneca, Biogen, Celgene, Genetech, Merck-MSD and Pfizer) in the form of periodic milestone payments and 1/3 from the Finnish Government's business and innovation fund (Business Finland, formerly TEKES). In late 2018, two additional pharmaceutical partners (GSK and Sanofi) were added and, according to the established governance plans, back-paid the milestone payments from the beginning of the program.

Why did pharma partners invest in FinnGen? What do they get out of it?

Though only one year in, we can begin to reflect on what elements of the project seem to be of greatest value to our industry partners. Some are less obvious than others and while many are specific to this project, there are elements in each that surely are much more broadly to other academic-industry partnerships.

1. **Participation in Project Design:** FinnGen offers the opportunity for partners to participate start-to-finish in the construction and use of a unique population health resource. Clinical working groups in seven major clinical areas (cardio-metabolic, gastroenterology, neurology, oncology, ophthalmology, pulmonology, rheumatology) combine leading Finnish medics and researchers with pharma clinical experts to actively design the definitions of endpoints and phenotypes from the available registry data, and to define together innovative ways of exploring the data. Genetic analysts work together with experts at FIMM and the Broad Institute on the design and execution of cutting-edge genetic analyses. And at the highest level, the project priorities and direction are set by a management committee with equal representation from pharma partners and academic/biobank scientists. This active weekly participation at multiple organization levels ensures the project will be focused on delivering insights relevant to day-to-day decision making in industry.

2. **Data access:** Obviously the major investment in the project goes to recruitment of patients from clinics throughout Finland and to their genotyping and analysis after samples have been entered into the national biobank and cross-linked with the extensive medical registry data. Partners get access to FinnGen data in two primary ways. They have real-time access throughout their organizations to all results emerging from genetic analyses designed by the academic-industry clinical working groups and genetic analysis teams in user-friendly web tools with links to many other supporting databases and other biobank genetic results of relevance. They further have secure cloud access to individual level data resources of the project in order to prosecute bespoke genetic analyses, integrate their own data, and utilize their own analysis methods. This access is provided using modern cloud computing and security which enables analysis of the data but prevents download of the individual level medical and genotype data.

3. **Access to expertise:** Another benefit that makes FinnGen attractive to industry partners is that it is designed by, and provides unfettered access to, top experts in human genetics. The human genetics history at FIMM is among the top in Europe (with longstanding contributions to genetics and epidemiology from Drs. Palotie, Kaprio, Groop and others) and the expertise in human genetics study design, analysis and execution from Dr. Daly's lab and partners at the

Broad such as Dr. Neale and at FIMM with Drs. Ripatti and Pirinen is at the top of the field. With the FinnGen analysis team housed at the Broad Institute, and Drs. Daly and Palotie maintaining labs in both locations, the decades long productive collaboration between the two institutions and their pre-cursors provides a collective insight for not only the design of FinnGen, more generally for the use of genetics for biological insight and the generation of therapeutic hypotheses.

4. **Access to unique recall phenotype and clinical trial potential:** In constructing a pre-competitive resource, industry partners are not simply helping to perform a landmark genetic study. In fact, the full value of the resource, given the progressive biobank law, is in the fact that all individuals can be recalled for any future approved research or clinical study. Already studies of physiology and response to therapy and vaccination are being designed to pursue the impact of specific functional variants discovered in the population – and the unique longitudinal data resources in conjunction with a large, genetically profiled population, enable risk prediction in a uniquely powerful way and, with the recall potential, will make Finland the ideal setting for primary prevention trials in the future.

5. **Joint formulation of new initiatives:** In the active weekly teleconferences and quarterly face-to-face meetings, ideas for how the project can be expanded or used as a launching point for new academic-industry activities is often discussed. For example, project funding was recently allocated to expand analysis activities to develop and support a global biobank meta-analysis to build a rapid network for follow-up of results and to, in many cases, provide a genomewide scan of certain clinical endpoints far larger than any published and available – yielding new insights. Among the groups FinnGen has begun coordination with are Biobank Japan, UK Biobank, Estonia Biobank, Generation Scotland, and four US-based hospital system biobanks and this has already in early stages proved productive in pursuing new FinnGen findings.

How does participation happen in practice?

Each industry partners provides representatives to a variety of working groups:

- **7 clinical working groups** in the aforementioned clinical areas along with Finnish national clinical experts in those areas to discuss endpoint definitions, study designs (these each meet on their own schedule and industry partners participate in as many as they choose)
- An **analysis committee** (Every other Tuesday, 9 am EST/4 pm EEST) that designs and implements core analysis pipelines and workflows, discusses and evaluates methodology and software options, reviews chip design, genotype QC, statistical analysis results
- A **scientific committee** (The alternating Tuesdays, 9 am EST/4 pm EEST) which discusses overall project strategy, evaluates and approves study design and execution decisions, reviews analyses and results and frames them in broader global or organizational context – receives updates from clinical and analytic groups
- A **steering committee** (Monthly, two hours, 10:30am EST / 5:30pm EEST) which is the decision-making body of the FinnGen Consortium through which plans, new initiatives and spending are approved; sets strategic direction for the entire project – a formal representative for voting purposes is named from each industry partner and each participating Finnish biobank

- **Face-to-face meetings:** Plenary meetings of all involved in the consortium take place twice a year (in first two years, there have been in March in UK (hosted by a Pharma partner, it just happens the first two will have been in UK) and September/October in Helsinki) in which all partners and Finnish biobanks have many representatives from all working areas. We also have had 2 smaller face-to-face meetings for specific topics or strategic planning at other times during the year (generally one at Broad Institute, one in conjunction with the ASHG Annual Meeting)