INDUSTRY
I-PWG
PHARMACOGENOMICS WORKING GROUP

DATE: 24 June 2021

TO: Israel Ministry of Health, Ethics Committees

FROM: Industry Pharmacogenomics Working Group (I-PWG)

SUBJECT: Comments on MoH General Management Notice regarding:
"Disease-Causing Variants in Actionable Genes that are Discovered Incidentally within the Framework of Genomic Research"

The Industry Pharmacogenomics Working Group (I-PWG) was established in 2000 and is comprised of functionally diverse members from pharmaceutical and biotechnology companies who engage pre-competitively to address emerging issues related to pharmacogenomics. Our mission is to improve patient care through integration of pharmacogenomics in drug development

The I-PWG is grateful to the opportunity to provide the enclosed recommendation in response to the General Management Notice referenced above which covers the return of incidental genetic findings in the context of a research setting.

I-PWG Recommendation:

I-PWG strongly encourages the MoH to allow for exemptions from the obligation to return incidental genomic results generated from biospecimens collected during clinical trials.

In particular, the following are situations in which returning incidental findings from genetic/genomic research are not appropriate:

1. When data is generated in non-accredited laboratories and/or from assays lacking appropriate clinical validation
2. When genomic research conducted as part of a clinical study for exploratory research purposes

Key Considerations for I-PWG recommendations:

The purpose of genomic research conducted as part of clinical trials (i.e. research purposes) is fundamentally different from genetic testing conducted for clinical care and medical decision making (i.e. diagnostic purposes). Clinical trial research is performed to explore the relationship between genetic markers and response to the study interventions, as well as to explore mechanisms of the disease indication of the trial. This work is important to improve future therapies for patient populations and it is not intended for individual patient diagnostic purposes. The American College of Medical Genetics (ACMG) publications provide guidance for reporting secondary findings when exome or genome sequencing is performed actively for clinical diagnostic purposes in appropriately accredited laboratories. Specifically, in the disclaimer of the publications, it states the intent is an "educational resource for medical geneticists and other health-care providers to help them provide quality medical genetic services". **Furthermore, ACMG has strongly discouraged the use of the recommendations for purposes other than reporting of incidental findings after clinical sequencing**.

- Although incidental genomic data may be embedded within the research database, there is no intent to directly analyze the database to find individual level data for medically significant mutations.
- Genomic research data are generally analyzed and evaluated in aggregate for the entire study population to understand if any common genetic features rise to the level of significance for association with the endpoint of interest. Therefore, incidental findings at the level of an individual study participant data are not expected. In contrast, analyses conducted for diagnostics purposes have a significantly higher level of rigor to provide individual level data that are reportable using a format appropriate for clinical interpretation.
- Clinical trial researchers are not typically trained or qualified, nor is the infrastructure usually available, to provide individual- level data back in an appropriate manner to medical professionals or patients for patient care decision making.
    - Genomic data generated and interrogated in the research environment is for research use only and are often performed in laboratories that are not appropriately regulated for return of information to study participants (e.g. CLIA certified in the United States). In contrast, genetic testing for clinical care is performed using validated methodologies in regulatory compliant laboratories, specifically designed for patient care. As such, we believe it is inappropriate, and in fact not lawful in the United States, to return genomic research results for patient care or medical decision making.
- Genomic research analysis using clinical trial biospecimens is often performed retrospectively after clinical trial completion when study participants are no longer active in the trial. In contrast, genetic testing data for clinical care is reported based on a diagnostic test (rapid turnaround). Thus, the return of genomic research results is limited in its ability to provide timely benefit to study participants in terms of the diagnosis, prevention, and/or greater awareness of disease predisposition.
- Clinical researchers may not have the infrastructure to report findings to study participants in an appropriate way. Significant resources would need to be diverted, for example to build compliant bioinformatics pipelines and hire additional genetics experts, including requirements for genetic counseling locally.
- The approach where study participants are clearly told in advance that results will not be returned and are encouraged to seek medical care and diagnoses from their regular HCPs would be more appropriate and ethical.

In closing, we believe that mandatory return of incidental genomic research findings generated from biospecimens collected in clinical trials is not appropriate and may have the unfortunate result of constraining the conduct of genetic research and innovative clinical studies in Israel.

Sincerely,

Industry Pharmacogenomics Working Group (I-PWG)

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About I-PWG:

The Industry Pharmacogenomics Working Group (I-PWG) was established in 2000 and is comprised of functionally diverse members from pharmaceutical and biotechnology companies. Our diverse membership is made up of those engaging in regulatory, statistical, technological, genomic and biological research as well as operations. We engage pre-competitively to address emerging issues related to pharmacogenomics.

The I-PWG follows closely the activities of the US Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMEA) other regulators and policy groups to ensure that its activities are relevant to their programs and needs. Among other steps, The I-PWG seeks to engage these bodies in discussion and information sharing and asks their continued assistance in identifying non-competitive issues about which the Group can provide information or other support.

Partner companies include:

AbbVie, Amgen, Astellas, AstraZeneca, BioMarin, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, CRISPR Therapeutics, Eisai, Eli Lilly, Gilead, GSK, Idorsia, Ionis, JNJ, Merck, Moderna, Novartis, Orion Pharma, Pfizer, Purdue, Regeneron, Roche, Sanofi, Sunovion, Teva, Valo Health, and UCB.