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The Precision Medicine Data Environment in Israel: A Review

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Introduction

Precision medicine (PM, a term used interchangeably with the older term "personalized medicine") is the embodiment of data-driven innovation. It harnesses intelligently the power of rich bioresources—collections of samples of human biological material and associated data—to develop individually tailored therapies in original ways. Whereas some samples and data are collected for the purpose of scientific research, the dominant portions of biosamples and data were originally (primarily) collected for purposes of medical treatment. Exploiting them to develop PM technologies is considered "secondary use."[1]

Given the vast amount of health information available and the growing recognition of the potential of such data and of the value of data sharing – large-scale projects increasingly involve multiple players, and data processing is becoming transnational, thus requiring cross-jurisdictional data transfer agreements (DTA). Whereas data environments that are similar in terms of their legal and ethical review frameworks potentially support and promote research using big health data, operating within data environments that are substantially different in these terms considerably influences the ability to conduct transnational research, to the point of inadvertently discouraging such initiatives, thus stifling innovation and preventing public benefit.

PM is an area in which the boundaries between research, clinical uses, and the healthcare industry are blurred. This creates novel regulatory spaces and challenges. It would appear, however, that PM-related regulatory challenges are variations on familiar traditional tensions—individual liberty versus solidarity and public interest in PM-derived benefit; autonomy versus paternalism; and risk versus benefit.

This concise overview introduces the legal and ethical environments of big health data (and genetic samples) in Israel, particularly as they relate to research. It also briefly addresses PM in Israel, identifies key stakeholders within the Israeli system, and reviews ethical issues associated with the use of big health data as well as some PM-

[1] Secondary use is the use of information or human biological materials (samples) originally collected for a purpose (typically, clinical use) other than the current one.

specific issues. Looking into other non-research big health data uses (for example, for marketing or for a health organization's internal control purposes) is beyond the scope of this review.

I. Precision medicine in Israel

PM is an innovative approach to disease prevention and treatment that takes into account genetic, biological, behavioral, and environmental variances between humans. PM uses big data analysis to tailor medical decisions, treatments, practices, and products to the individual patient. Featured as sensitive, individualized, and adaptive, PM has the advantage of an enhanced ability to predict how individuals will respond to various therapies.

Among the unique challenges of PM is its ambitious goal of customizing healthcare by identifying effective approaches for patients, based on genetic, environmental, and lifestyle factors, in an accurate and targeted manner (as implied by the word "precision").

The following unique features of Israel's health system and population have a significant bearing on the local data environment and make Israeli-based PM research and innovation particularly appealing.

a) A **unique and uniform identification number (uniform identifier)** – The existence of a uniform identifier (Israel is one of 16 OECD countries where individuals use such identifiers) allows **cross-referencing and linkage** of data about individuals from different repositories.

b) **Connectivity between databases** – Israel is one of 12 OECD countries that link medical information throughout the health-care chain. This is possible thanks to the application of a uniform identifier system. Such connectivity typically serves therapeutic purposes and continuity of treatment.

c) **Centralization of databases** – Israel has a relatively centralized health system, managed by the Ministry of Health (MoH). The Israeli public enjoys a highly efficient healthcare system and provides an extensive variety of health information that is linked to a uniform identifier. Electronic health records, in use in Israel since the 1980s, cover the overwhelming majority of the populace. About 70% of national

health databases are under the responsibility of the same organization, and about 80% are connected continuously. The centralization of databases reduces the need to link small, dispersed databases.

d) **A "genomic goldmine"** – Another characteristic of the exceptional quality of Israeli databases is the extraordinary variety of homogeneous populations that make up the Israeli public. Within a rather modest population of about 9 million, various origins are represented: Eastern and western Europe, Asia, Arab states, North America, and North Africa. The country's populace is a mix of Ashkenazi, Sephardic, and Ethiopian Jews; Arabs; Bedouins; Druze; and Circassians—with populations that are generally highly inbred. This leads to the multiplication of genetic mutations, but it also serves as fertile ground for research.

e) **An innovative environment and extensive entrepreneurial activity** – These factors, briefly referred to below, coupled with Israel's longstanding scientific excellence are significant drivers of PM developments, indirectly influencing the local data environment.

Despite these unique and advantageous features, an OECD report from 2013 examining the availability and use of information from health databases in member countries, found that whereas connectivity and current use of health information in Israel is relatively high, and Israel is one of the most advanced countries in the field with regard to various parameters, the country is ranked very low on the availability of information for research purposes. Access to information for researchers in academia or in commercial entities—for use in R&D and for linking it to various sources—is limited. The report indicates that Israel fails to exhaust the potential of health information for research purposes and policy making in the health-care system. This may change, however, as the regulatory regime concerning big health data undergoes the revisions described below.

National PM-promoting initiatives

Israel, like the United Kingdom, other European states, and North America, is allocating vast resources for the development of PM technologies and supporting infrastructure. The following are a few examples:

a) **National Digital Health Plan** – Israel has set up a National Digital Health Plan to create a digital database of the medical records of its roughly 9 million residents, and make them available to researchers and health initiatives. The integration of Israel's genomic and clinical data with its computational capabilities, has great research potential.

b) **The Mosaic Project** – This project, a national information infrastructure for health research in the fields of genetics and medical information, is a product of collaboration between various government ministries and entities. The project is designed to operate on three main levels—scientific, medical, and economic—through three basic components: 1) **a community** of volunteers suffering from complex diseases and/or medical conditions for which no effective treatment has yet been found, who will knowingly share clinical information; 2) **genetic** and other **information**; and 3) **information infrastructure and research tools**. This new genomic and clinical data infrastructure of an engineered repository is designed to serve researchers from academia, health organizations, and industry (for the development of health products and services). The Mosaic database enables research on unique population cuts and research manipulations for developing groundbreaking technology to treat diseases such as cancer, celiac, autism, heart disease, stroke, diabetes, and Crohn's. The project's aim is to strengthen Israel's comparative advantage in the long-term digital documentation of its population's health information.

Local PM innovations and initiatives

Israeli PM innovations include drug discoveries, (automated) diagnostic tools, and disease prediction tools. Here are a few examples:

- **Maccabi Healthcare Services HMO** has developed an AI system that can predict the presence of colon cancer on the basis of a simple blood test. It has also been developing tools to personalize drug treatment for hypertensive patients, using big data accumulated in the organization.

- **Clalit HMO** has been developing tools to monitor diseases and predict acute myeloid leukemia risk.

- **FoundationOne**
    - *FoundationOne Liquid* – A unique blood test (liquid biopsy) for identifying and adjusting targeted treatment for cancer patients, offering the possibility of genomic diagnosis to patients who cannot undergo surgical biopsy. The test separates the DNA from the patient's blood and can accurately identify all relevant mutations in 70 genes with optimal sensitivity and accuracy for all mutations, thereby helping to determine whether the tumor contains genetic changes that may respond to goal-oriented therapy.
    - *FoundationOne genomic diagnosis predicting response to immunotherapy* – Tests that make possible genomic diagnostics, which simultaneously identify a large number of genetic mutations and even certain markers. Finding these markers during a comprehensive genomic diagnosis can help identify patients who may respond to new immunotherapy.

- **ImmPACT-Bio** – A CAR-T personalized technology (a treatment in which a patient's T cells are modified to attack cancer cells) under development, based on bioinformatics tools and databases of patients' samples.

- **CytoReason** – Machine-learning models applied to biological data of the immune system to discover new drugs.

- **ZebraMed** and **AIdoc** – An automated radiologist solution, developed as a support tool for medical providers via data and diagnostics, in light of the growing shortage of doctors and medical staff.

2. Key stakeholders within the Israeli system

a) The Israeli public

The Israeli health-care system is universal and financed through health taxes paid by the public. Thus, the latter indirectly funds the very system that enables public health organizations to gather health information. The public not only contributes to funding data collection, it is also the selfsame source of such information. Although the basic assumption is that an individual patient's medical record belongs to him or her, health organizations may collect and use information about patients because this is deemed consistent with the public interest (provided that

the public's interest in protecting its privacy and autonomy with respect to the secondary uses of health information is upheld). Being providers of both (some) funding and health data creates, therefore, a correlative public expectation of partaking, on an egalitarian basis, of benefits accruing through the secondary uses of such information and from its products as well as from innovation in public health organizations.

Recognizing the Israeli public as a player of paramount importance, the MoH supports and promotes an explanatory process, a process of public participation, and increased transparency regarding the secondary uses of health information.

b) **Patients, patient advocacy groups, and research participants**

Specific members of the public—groups or individuals—with direct health interests in, and needs for, PM technologies are patients. Patients with complex diseases lacking effective treatment to date have high expectations of PM innovative medical solutions to ameliorate their lives, and improve their functioning and wellbeing. Patients, inter alia as research participants, are increasingly expected to be active participants in PM, rather than passive subjects or recipients of its benefits, and are somewhat burdened by such expectations of engagement. Patients are not only targeted "consumers" of PM, they are also the very source of health information and the providers of data used in the development of PM technologies. Their unique *sine qua non* contribution to PM, carries expectations of benefit sharing (through researchers and biotech or pharma companies).

c) **The state, via relevant government bodies** (the MoH, the Ministry of Finance, the Ministry for Social Equality, and the Prime Minister's Office)

The state is the entity that holds health information, using it mainly to determine policy. The state is interested in promoting the use of health information to improve medicine and create economic value, while promoting the public's interest in protecting its privacy with respect to such information. Expanding the accessibility of information in the health system in order to improve treatment within the system and save system resources, is another aim of the state. The state is also interested in developing an ecosystem for innovation in medical research and development through a high-quality medical information infrastructure, using the tool of big data. The government, through the MoH in particular, aims to achieve this goal by

advancing a National Digital Health Plan, which it perceives as a national growth engine with the potential to promote innovation and create such an ecosystem.

1. **The Innovation Authority**

The Innovation Authority promotes the development of innovative technologies for the benefit of the Israeli public, partly by facilitating international scientific collaboration. It aims to realize in various ways Israel's competitive advantage in an age of personalized medicine. It is a co-partner in the Mosaic Project and is establishing users association—including start-ups, multinational companies for digital health, and mid-to-large cap companies—to serve as a network of medical data infrastructure (a project funded jointly by the national Digital Israel Initiative in the Ministry for Social Equality). The objectives of such an association are sharing new and existing medical data, making the data accessible, and establishing regulatory infrastructure and information security. The program will work in collaboration with academic and clinical Israeli entities, as well as with international entities.

d) **HMOs** (Health Maintenance Organizations)

The Israeli public is medically insured and receives health services from one of four health-care providers (HMOs): Clalit, Maccabi Healthcare Services, Meuhedet, and Leumit. The HMOs have been collecting health information electronically for over 20 years. Their databases contain broad information on a large number of patients, on an international scale. Two of the HMOs, Clalit and Maccabi (which insure approximately 50% and 25%, respectively, of the Israeli population), invest substantial resources in developing the collection and use of the information in their possession and operate research institutes. Consequently, each of the HMOs perceives the databases in its possession as an exclusive asset, in the creation of which considerable resources have been invested. Each HMO seeks to use the health information in its possession to promote research and innovation within the organization, as well as to improve its efficiency and the medical treatment it provides. Therefore, health information assets have financial value, and HMOs are interested in trading in them to create additional budgetary sources that will enable them to continue investing in the development of their databases. HMOs, as data controllers, also have a vested interest in the Mosaic Project.

e) **Hospitals**

Hospitals in Israel collect information accumulated in the course of medical treatment and care during hospitalizations, with considerable variation between hospitals and the departments in them with regard to information system practices (from none, through hard copy, to digital). Some hospitals make extensive use of the information in their possession, promoting innovative research, while some do so on a smaller scale. As is the case with the HMOs, it is in the hospitals' interest to promote innovation within the hospital, improve the quality of health-care provided, and create sources of income.

f) **The biotech and pharma industries**

Technology companies require health information and data to produce and commercialize innovative products that stand to generate economic profit. Identifying significant economic potential in health information, companies invest heavily in procuring and collecting it. Biotech companies use big data methods to develop data collection and analysis infrastructures. To access existing information collected during medical treatment, technology companies enter into cooperation agreements with health organizations and states. In exchange for access to health information, such companies tend to grant the organization or the state rights to use the company's products and the ability to influence the development processes of the products.

International pharmaceutical companies operate in Israel through local representatives, often conducting clinical trials. This generates interest in expanding access to information collected in the health system for various research purposes. Using such information and data can help in identifying specific groups of potential participants in clinical trials, identifying medical needs and demand for the development of drugs to help treat various conditions, and learning about drug consumption.

g) **Academia** (researchers and academic institutions)

Researchers, by the very nature of their occupation, are information consumers, and their academic freedom often depends on access to health data and biosamples. Given the limited resources available to academic and research bodies, these entities have an interest in accessing information in exchange for creating research value for

the information provider, while retaining the right to publish the results of their uses of data and information and keeping the intellectual property rights concerning products produced by research-generated knowledge. Access to health information by academic researchers is presently largely unstructured. It may be granted by personal or local cooperation initiatives with health-care organizations or by cooperation agreements between academic institutions and health organizations.

h) **Medical service providers**

Privately owned medical service providers, such as institutes and clinics, collect health information in the course of providing medical care. Some of that information is transferred to the patient's HMO to ensure continuity of treatment, but much health information (e.g., medical records and test and imaging results) remains with medical service providers and is not shared with HMOs. Linking the information collected by the various providers stands to augment the therapeutic continuum within the health system and to generate considerable research value.

i) **Insurance companies**

Insurance companies have great interest in health data concerning Israel's population. Such data can be used by companies to tailor insurance products offered to the public. The data can also lead insurance companies to toughen the conditions for coverage or to collect higher premiums for at-risk populations.

3. Regulatory background

A. The current regulatory landscape

In Israel, as in other developed jurisdictions, PM is not subject to specific regulation, in and of itself. It is commonly accepted that novel medical technologies in the making, still in the research phase, cannot (for pragmatic reasons of epistemic uncertainty and difficulty in predicting their effects and medico-social consequences), and indeed *should not*, be regulated through dedicated, technology-specific legislation, given that innovation and scientific developments typically outpace regulation.

PM is therefore indirectly (nonspecifically) regulated by the wide body of existing laws and other regulatory instruments governing other applications of clinical care and

medical research. Such regulation creates a fragmented regulatory setting for PM and the satellite issues of big (health) data and clinical research.

The following is a concise overview of the current regulatory landscape concerning various aspects that are directly or indirectly related to PM.

Clinical research

In Israel, clinical research trials in humans—the obligatory route to practicable, effective, and safe PM—are not regulated by primary legislation but rather by means of various mechanisms, primarily the **Public Health Regulations (Clinical Trials in Human Subjects) – 1980** ("Clinical Trials Regulations"). These regulations define medical experimentation on humans and set forth the terms and stages for review and approval of clinical trials in human subjects by institutional review boards (IRB) and by the Supreme Helsinki Committee for Medical Experiments on Human Subjects ("Supreme Helsinki Committee"). Importantly, the Clinical Trials Regulations incorporate into Israeli law the Ethical Principles for Medical Research Involving Human Subjects, laid out in the WMA Declaration of Helsinki (see, the First Schedule).

Research approval mechanisms

PM research typically (even inherently) includes a genetic arm. Such research requires two-tiered approval: *(a)* preliminary approval by the **IRB** (namely, of the director of the medical institution); and *(b)* the opinion of the **Supreme Helsinki Committee**, as a precondition for approval by the MoH Director-General, for a research that constitutes "an experiment involving a person's genetic makeup" (Clinical Trials Regulations, s. 3b.).

Approval mechanisms for establishing a genetic biobank

The *collection* of genetic samples (a pool of 1,000 or more samples for research and medical purposes), their *use*, and the terms for *sharing* are specifically regulated by the 2005 **Director-General (MoH) Circular No. 01/05 — "The Establishment and Utilization of Genetic Samples Banks**." Establishing a genetic biobank or conducting research on already deposited genetic samples and associated data, similarly requires two-tiered approval (IRB and the Supreme Helsinki Committee).

Establishing such a biobank requires a designated research request accompanied by an informed consent form and an information sheet that addresses such matters as the purpose of the biobank, the nature of the material to be collected, conditions for the use of samples (rules of access), privacy protection measures applied, and reference to ethical aspects and risks associated with participation in the biobank.

These requirements seem to be generally consistent with the principles stipulated in the WMA Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks.

By contrast, in the United Kingdom, NHS Health Research Authority (HRA) approval is *not* required for the establishment of research *tissue banks* (RTB), although an ethical review of the arrangements for collection, storage, use, and distribution of tissue, may be sought on a voluntary basis by organizations responsible for the management of RTBs.
HRA approval is similarly *not* required for the establishment of research databases.
Again, an ethical review of various aspects, including collection, storage, use, and distribution of data as well as arrangements for the release of *non-identifiable* data for analysis by external researchers, is voluntary.

Approval mechanisms for research conducted on health data
According to the 2006 **Director-General (MoH) Circular No. 15/06—Helsinki Subcommittee for Approval of Research That is Not a Medical Experiment in Humans** ("Helsinki Subcommittee Circular"), studies of data collected from medical, nursing, psychological and other records without involving patients that are strictly a secondary data analysis in which investigators never interact with participants, do not constitute a clinical trial in humans.

The circular creates a somewhat expedited route for the approval of research restricted to data analysis that is deemed to be of *minimal risk*. This represents the currently applicable legal and policy instrument for research using big health data.

In the United Kingdom, Research Ethics Committee (REC) approval is required by law, where the activities of a research database stand to include accessing or otherwise

processing the *identifiable* data of patients or services by users outside the normal care team (that is, for secondary use) **without consent**. Such research would also require an application to the Confidentiality Advisory Group (the NHS Act 2006, s. 251) in order to set aside the common law duty of confidentiality owed by care professionals to their patients (Standard Operating Procedures for Research Ethics Committees, s. 11).

In the United States, secondary research with *nonidentifiable* private information or biospecimens (namely, irrevocably anonymous information or human materials, where the data set contains no identifiers, either direct or linked by code) is not considered research on human subjects and therefore does *not* require IRB review. IRB review is generally required for research involving secondary use of *identifiable* information or human biological materials.

Under the Federal Policy for the Protection of Human Subjects (also known as the "Common Rule") some secondary research uses of identifiable private information or biospecimens are considered "**exempt research**," meaning that they are absolved of adhering to said policy (including the requirement for consent) where certain conditions are met (§46.104).

This applies to secondary research uses of identifiable private information or biospecimens where:

(i) the identifiable private information or biospecimens are **publicly available**; or

(ii) the information is recorded by the investigator in such a manner that **the identity of the human subjects cannot readily be ascertained directly or through identifiers**, [and] subjects shall not be contacted or re-identified by the investigator; or

(iii) the research involves only **information collection and analysis** involving the investigator's use of identifiable health information, for **purposes of health-care operations, research, or public health activities** and purposes.

(iv) The research is conducted by, or on behalf of, a **federal department or agency using government-generated or government-collected information obtained for non-research activities** and generates identifiable private information that is or will be maintained on secure information technology systems.

Certain exemptions require **limited IRB review**, in which the IRB is absolved of considering all of the approval criteria, and the requirement for ethical review is satisfied by a determination that certain conditions, specified in the regulations, are met.

An IRB may use the **expedited review** mechanism (by the chairperson or an experienced IRB member designated by the chairperson) (§46.110) to review the following relevant research, for which limited IRB review is a condition of exemption:

- **Storage or maintenance of identifiable private information or biospecimens** for potential secondary research use (for which broad consent is required), where the required determinations to evaluate the appropriateness of the broad consent are made;
- **Secondary research involving the use of identifiable private information** or biospecimens, if **broad consent** for the storage, maintenance, and secondary research use was obtained.

Consent

In general, the requirement for informed consent for participation in medical experiments is embedded in the Clinical Trials Regulations, which incorporate the WMA Declaration of Helsinki ethical principles. The required components of informed consent are stipulated in the **Patient Rights Law – 1996** (s. 13).

More specifically, the taking and genetic testing of DNA samples (for research or clinical purposes) requires the subject's consent, according to the **Genetic Information Act – 2000** (s. 11(a)).

Waiver of informed consent

1. Research on health data

In health data research in which data are collected without involving patients, the subcommittee may exempt the investigator from acquiring informed consent, provided that the information is *fully anonymized* (Helsinki Subcommittee Circular).

2. Retrospective studies (on genetic samples)

The requirement for informed consent may be waived for retrospective research, that is, research on previously collected genetic samples, provided anonymization is

guaranteed, according to the **Genetic Information Act – 2000** and the **Guidelines for Clinical Trials in Human Subjects of the Ministry of Health (2016)** ("Guidelines for Clinical Trials").

The following slightly nuanced cases may enjoy such exemption:

- Experiments using only *unidentified DNA samples* or using *existing* DNA samples stripped of all identifying information;
- Experiments using existing *unidentified* human *biological* samples;
- Experiments using samples collected prior to the date of entry into force of the Genetic Information Law – 2000 (i.e., December, 2001);
- Experiments using samples taken from an existing and approved biobank, on condition that sample providers have previously consented to the use of their samples for any future legally approved research.

In the United States, under the Common Rule, for research that is essentially a secondary data analysis, namely, *minimal risk* research, the IRB may approve (through a limited, expedited review procedure) a request to waive some or all of the required elements of informed consent (45 CFR 46.116(f)). To waive entirely or to alter informed consent elements, the IRB must determine that:

(i) The research involves no more than minimal risk to subjects;

(ii) The research could *not* be carried out practicably without the waiver or alteration;

(iii) The research involves identifiable private information or biospecimens and could not be carried out practicably without using the information/specimen in an identifiable form [a requirement added in 2018];

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and,

(v) Where appropriate, the subjects will be provided with additional pertinent information about their participation.

Data sharing

A clinician or medical institution may transmit or release medical or health information to another, inter alia for research purposes and for publication in a scientific journal,

provided that no patient identifying information is revealed (see **Patient Rights Law – 1996** (s. 20(a)(7)).

The Genetic Information Act – 2000, representing a genetic exceptionalism approach, specifically addresses the transmitting of genetic information for research purposes. According to s. 23 therein, a person/organization holding genetic information or a genetic database may transmit the information in his possession for purposes of legally approved research, or publication in a scientific journal, on condition that (1) the genetic information is transmitted without any identifying detail; or (2) the individual data subject has consented in writing to the transmission/delivery of genetic information. Disclosure of identifying information in a scientific publication is prohibited, unless the individual data subject has provided explicit written consent beforehand.

In the United States, the National Institutes of Health (NIH) has a rather developed data sharing policy in place, endorsing the sharing of final research data for research funded by the NIH (and other national agencies and initiatives). Particularly relevant is the **NIH Genomic Data Sharing Policy**, aimed at facilitating the sharing of genomic data as well as phenotypic and other associated data generated in NIH-funded research by requiring that such (de-identified) data be submitted to an NIH-designated data repository.

In the United Kingdom, too, data sharing is encouraged in the interest of maximizing the research potential of existing data. Accordingly, external researchers may be granted generic approval to access *non-identifiable* data. Release of data extracts to external researchers must meet several conditions (Standard Operating Procedures for Research Ethics Committees, s. 11):

- Research must be conducted in a manner that guarantees that data subjects are unidentifiable to external researchers, and data extracts must be effectively de-identified prior to release;
- Researchers must treat data sets in confidence and not attempt to re-identify data subjects through linkage with other data;
- Data sharing agreements with researchers must be in place.

Transfer of samples to international research partners

Release of samples from the biobank shall be permitted only for (legally approved) research purposes. The transfer of samples and/or data overseas is subject to the approval of the Supreme Helsinki Committee, in accordance with its instructions and the provisions of the **Privacy Protection Regulations (Transfer of Information to Databases Outside the State's Boundaries) – 2001**, regulating, inter alia, the transfer of data to international research partners. These regulations apply certain conditions to the transfer of data from databases in Israel. First and foremost, they stipulate that the law of the country to which the data are transferred ensures a level of information protection that is no lesser, mutatis mutandis, than that provided for by Israeli law. The law of such a country must provide for a legal and fair collection and analysis of data, accurate and updated data, a purpose limitation (data shall be held, used, and delivered only for the purpose for which it was received), the right of individual data subjects to review personal information and have inaccurate information corrected, and a duty to take all necessary security measures to protect the privacy of information in databases.

Notwithstanding these conditions, the owner of a database may transfer information or permit the transfer of information from his or her database in Israel outside its borders if the following alternate relevant conditions, apply: (a) the individual data subject has consented to the transfer; or (b) the consent of the data subject cannot be obtained and the transfer is vital to the protection of the subject's health or physical wellbeing; or (c) the information is transferred within the framework of a DTA that contains a commitment to comply with the conditions for the maintenance and use of information applicable to a database in Israel, mutatis mutandis; or (d) the information is transferred to a database in a country that is a party to the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, inter alia.

When transferring data overseas, the owner of the database shall ensure, through a letter of cooperation with the foreign researcher/institution, that the latter is taking adequate measures to ensure the privacy of the data subjects and guarantees that the data shall not be transferred to any third party.

As a rule, **identified samples shall not be transferred overseas**, unless this is essential for duly approved research, in which case all identifiers shall be transmitted in an *encoded* format, with the coding key retained in Israel.

These requirements are also specifically anchored in the Guidelines for Clinical Trials (s. 6.2.7), which are in compliance with the WMA Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP E6).

Privacy protection for health databases

Personal data and individual health data are considered "sensitive information" under the **Protection of Privacy Law – 1981**, thereby meriting a higher level of privacy protection. Chapter Two of the Protection of Privacy Law sets forth the provisions for the protection of privacy in databases, including mandatory registration with the registrar of databases of any database containing sensitive information, holding information on more than 10,000 persons, belonging to a public body, or having other specified characteristics.

In accordance with the data protection environment promoted by the EU **General Data Protection Regulation (GDPR)** pertaining to the processing of personal data of individuals, which came into force last May, a further specific layer of protection was added (in the period prior to its coming into force) by the introduction of the **Privacy Protection (Data Security) Regulations – 2017** ("Privacy Protection Regulations"). These regulations specify comprehensive data security obligations for databases and they apply in a sweeping and binding manner to any activity of processing personal information that is subject to Israeli law, in both the public and private sectors.

The regulations stipulate security level categories for databases, in accordance with their size and the nature of the information they contain. Databases that contain medical information, information regarding a person's mental condition, or genetic information are essentially categorized as "databases subject to a medium security level" (First Schedule). Databases containing the same type of information regarding 100,000 persons or more, or databases for which the number of persons authorized to access this information exceeds 100, including a database of a public body, are categorized as "databases subject to a high level of security" (Second Schedule). Stricter controls and data security measures must be applied to databases belonging to these two categories, and appropriate obligations are imposed upon database controllers to

prevent unauthorized use of data held therein, which is considered a "severe security incident".

These regulations came into effect in May 2018, around the same time as the GDPR. Israel has taken some regulatory steps to comply with the GDPR. Therefore, when the GDPR became applicable, Israel was included in the list of third countries that ensure an adequate level of protection for personal data and data transfer to Israel was expressly permitted. Naturally, this has important bearings on the ability of Israeli researchers to take part in the international exchange of health data, thus—together with the revised secondary research regulatory regime described below—facilitating interoperability in this area.

B. Revisions in the big health data secondary research regulatory regime

1) The MoH Committee for the Implementation of the Recommendations for Secondary Uses of Health information

Recognizing the enormous potential inherent in big health data and the advantages of sharing health information gathered by health organizations with local and international academic and industry research bodies, in 2016 Israel's MoH appointed a public committee to examine the implications of, and provide guidance for, secondary uses of big health data. The committee published its recommendations in January 2018, and two MoH (Director-General) circulars regarding them were released nearly simultaneously.

The committee's recommendations are serving as a basis for reformulating specific regulation of secondary uses of big health data. The committee sought to balance the public's interest in the use of health information and sharing of its related research benefits, the rights of individual data subjects to protection of their privacy and autonomy, and the interests of data collectors and researchers in making the data accessible. The committee recognized the investment of collectors/controllers in health data, in terms of the resources put into collecting, processing, or analyzing them, as well as their potential intellectual property interests in innovations based on health data. It recommended a framework for appropriate incentives to promote the secondary use of health data for the benefit of the public. Such incentives are aimed at encouraging a multi-faceted flow of information that will serve the entire health system, shortening

approval processes, streamlining the transfer of information between organizations, and more.

The following is a short summary of pertinent recommendations delivered by the **Subcommittee** (one of four, under this committee) **for Defining a Code of Ethics** (hereinafter: "The subcommittee"):

- *A designated approval mechanism*

The subcommittee developed a set of rules for approval of secondary uses of health data. Among them is the establishment of a designated approval mechanism for secondary uses of health information, to review the designed process and examine the various aspects of the requested secondary use. It recommended that a mechanism such as an **ethics committee for information use** be integrated into the existing subcommittee for the approval of noninterventional studies in humans, mutatis mutandis, introducing, for example, a mechanism for publicly transparent decisions and including relevant expert professionals skilled in technology, information security, and de-identification.

According to these rules, uses of research information will require individual approval by the ethics committee for information use. Such approval will be valid for up to two years from the date access to the data is granted. Any organization or person granted access to the data shall be fully responsible for maintaining the privacy of the individual data subjects.

- *Data accessibility and consent*

In general, in order to increase the opportunity for data use and in the interest of fairness, the following was recommended: *a)* **Facilitate access** to data for low-resource players representing the public interest, such as academics, nonprofit organizations, or start-up companies; and *b)* **Prohibit exclusivity** in the use of secondary health data collected by the way or as part of medical treatment or service, in the interest of data sharing and non-exclusion of researchers (save for circumstances in which such data had been a priori collected at the request of an external organization or person, with their own funding or investment, where granting exclusivity for data use, for as short a period as possible, might be considered).

Regarding the required consent (opt-in/opt-out/exemption) to access to health data, the recommendations reflect a relative approach, depending on the level of data identification (identified/de-identified/aggregated):
As a rule, access to *identified* information for secondary use purposes should be as limited as possible and require an *opt-in* consent mechanism, that is, explicit individual consent (with the exception of making data accessible to the MoH for public health monitoring purposes, which ought to be exempt from the consent requirement). This is obviously due to the significantly increased risk to patients' privacy posed by the non-anonymity of such health information.

As for *de-identified* health data, organizations may make it accessible to external institutions *exclusively* for the following purposes: *a)* research, *b)* determination of health policy, *c)* evaluation of health policy, and *d)* improvement of health policy.

Using *de-identified* data minimizes the risk of identification and compromise of patients' privacy and may therefore be approved *without* requiring the consent of individual data subjects for making the data accessible to an external party.

Given the strong presumption that aggregation can secure a rather high level of anonymity, organizations will be allowed to make *aggregated* health data accessible for *any* other purpose, provided that it complies with the ethical principles guiding the subcommittee's work. Also, since properly aggregated data present a negligible risk to the individual data subject's privacy, patients' **consent is not required** for the secondary use of such data, or for making it accessible, if such use was approved by the designated approval mechanism (through an *expedited* process), following confirmation that the purpose of the requested use or its probable outcome will not result in harmful stigmatization or discrimination of any group or individual.

It is recommended that health data made accessible to external organizations for any purpose will be *aggregated*, unless the patient has fully consented to the following: processes necessary for the provision of medical treatment or service, research, health policy determination, health policy evaluation, health policy improvement, and any mandated use required by law or by virtue of law.

According to the majority stance in the subcommittee, approving access to *non-aggregated* (identified/de-identified) data for external organizations, for marketing purposes, or for the purpose of making health data accessible to the public is deemed *inappropriate*, even where full consent is provided by the patient (individual data subject). Access to identified or de-identified data required *by law* or by virtue of the law shall be *exempt* from the requirement of consent.

The following table[2] summarizes and simplifies the triple relations between purpose of data use, level of data identification, and the type of consent required (opt-in/opt-out/exemption), for secondary use of data by *external* organizations or persons:

Purpose of data use	**Level of data identification**		
	Identified data	**identified-De data**	**Aggregated data**
Essential uses for the provision of medical treatment or service and/or ongoing operation of a health organization	Exemption from consent	Exemption from consent	Exemption from consent
Use for research or setting health policy	Informed consent (in-opt)	Exemption from consent or opt-out	Exemption from consent
Use for marketing purposes	Inappropriate use	Inappropriate use	Exemption from consent
Making health data accessible to the public	Inappropriate use	Inappropriate use	Exemption from consent
Use for executing the functions and powers of the MoH	Exemption from consent	Exemption from consent	Exemption from consent
Use required by law or by virtue of the law	Exemption from consent	Exemption from consent	Exemption from consent
Use for legal purposes	According to the law	According to the law	Exemption from consent
Any other purpose	Informed consent (in-opt)	Informed consent (in-opt)	Exemption from consent

[2] See: *Conclusions of the Committee for the Implementation of the Recommendations for Secondary Uses of Health Information*, MoH (January 2018), p. 75.
https://www.health.gov.il/PublicationsFiles/health_info.pdf

2) *Director-General (MoH) Circular No. 01/2018 – Secondary Uses of Health Information*

The MoH guidelines were considered and drafted, inter alia, in light of the OECD Recommendation of the Council on Health Data Governance, of January 2017,[3] concerning secondary uses of information, offering ways of formulating regulation and including suggestions regarding its content. These recommendations will be taken into account in the formulation of future regulation in Israel.

The aim of this circular was to define interim guidelines and rules for secondary uses of health information, in accordance with existing law, until the completion of relevant regulation.

The guidelines address issues of data de-identification, approval mechanisms for secondary use of health information, consent to secondary use of information, and rules for secondary use of health information.

Selected guidelines include the following:

- In the absence of legal approval or consent to the use of identifiable individual information, secondary use will be possible only for de-identified information (s. 5.3).
- The sharing and delivery of private health information between public bodies requires the approval of the Committee for the Transfer of Information, in accordance with the Protection of Privacy Law and in accordance with the provisions of the Privacy Protection Order (s. 6.3).
- Secondary use of health information for research purposes—sharing and delivery of health information, or access thereto, for the purpose of research—shall require the approval of the Ethics Committee, in accordance with the Public Health Regulations (Medical Trials in Human Subjects) – 1980, the Guidelines for Clinical Trials, and the Director-General (MoH) Circular No. 15/06 of the Helsinki Subcommittee for Approval of Research That Is Not a Medical Experiment in Humans (s. 6.4).
- Unless provisions are made in law that allow the use of health information without consent, secondary use of identified or identifiable information, in particular for research purposes, is conditional upon the receipt of free and informed consent of the patients, that is, individual data *subjects* (s. 7.1).

[3] Recommendation of the Council on Health Data Governance, OECD, January 17, 2017.

- The Ethics Committee may exempt an investigator from the need to obtain consent if the information is properly de-identified (s. 7.2).
- As a rule, for the purpose of secondary use of health information in the framework of research approved by the Ethics Committee, access to information in a secure environment within the organization (e.g., a physical or virtual "research room") should be provided, while avoiding the release of identified or identifiable individual information beyond the control of the health organization (s. 8.3).
- The release for research purposes of individual (de-identified) health information under the organization's control will be carried out in a manner that ensures a level of protection of information that is no less than the level of protection of information set in the MoH guidelines. Such release of information requires the reasoned approval of the Ethics Committee and the authorized body in the organization, addressing its necessity for that particular use. (s. 8.4).
- Any entity outside or within the organization that receives (de-identified) health information or access thereto for use, shall sign a commitment to preserve the confidentiality of the information, to prohibit actions and/or attempts to identify individuals by use of information, to use the information exclusively for the approved purpose, and to guarantee the non-transfer of information to any third party without the organization's approval (s. 8.6).

3) Director-General (MoH) Circular No. 02/2018 – Collaborations Based on Secondary Uses of Health Information

To enable the realization of the great potential inherent in big health data, the MoH is interested in encouraging cooperation between various entities, including bodies with limited resources that can advance medicine.

This circular outlines the framework for inter-organizational data sharing. In accordance with the circular, data use/data sharing agreements must comply with certain guidelines, including the following:

- **Specification, transparency, and purpose limitation** – The agreement shall clearly and transparently describe its purposes and the purposes of the use of the health information, and shall prohibit the use of health information for such purposes that

do not serve the promotion of care, medical service, public health, or scientific research in the field of health (s. 6.3.1).

- **Compliance with rules of ethics** – These include creating benefit to the general public or to a relevant patient group; prohibiting inappropriate discriminatory use; non-exclusivity (except for information collected at the sole request of the other party and financed or invested in by that party). In such cases, exclusivity shall be granted for a period of no longer than 18 months (s. 6.3.2).
- **Adherence to privacy, medical confidentiality, and information security** – This includes defining the use of technological and organizational means for information security and information privacy protection and defining formal processes for identifying and tracing risks (s. 6.3.3).
- **Rules governing the use of information** – The release of identified or identifiable information outside the control of an organization is prohibited without the consent of the patient subjects of that information (s. 6.3.4).

4. Ethical Issues Associated with the Use of Big Health Data

Privacy

Biobanks and health databases, which by their nature collect and hold sensitive identifiable information, challenge key privacy principles, in particular the principles of *purpose limitation* (as future secondary research purposes are unknown at the time of collection) and *data minimization* (limiting the collection and processing of personal information to that which is necessary and directly relevant to accomplishing a specified purpose). Various de-identification methods and restrictive rules regarding the transfer of identifiable biological samples or data are typically put in place to mitigate privacy threats.

Broad consent

Health databases and biobanks often opt for a "broad" consent model for participants. Such a type of consent pertains to collection, storage, maintenance, and secondary research with identifiable private information or human biosamples. This consent model, recently introduced into the United States' revised Common Rule of 2018 and recognized in the International Ethical Guidelines on Health-Related Research (of the Council for International Organizations of Medical Sciences [CIOMS]), is ethically controversial (although increasingly less so), because of its autonomy-imperiling quality. Though it is deemed necessary for robust and effective data sharing

(maximizing the potential for patient-related research) intrinsic to data-based secondary research, questions are often raised as to whether broad consent can indeed be informed. Its one-off, non-specific nature does not allow for specific consent to new research projects, making it a lesser form of consent. When consent is granted initially, at the point of entry to the biobank or health database, the specific research project using biosamples or data, respectively, is unknown (albeit more general research purposes can be envisaged), so research participants have no knowledge regarding the uses to which they are in fact consenting, and this arguably vitiates their autonomy. Critics of this approach argue that broad consent does not necessarily mean that it is vague or uninformed. Rather, it is a *choice*, a decision made by participants with appropriate understanding to allow others (biobank or health database controllers) to decide. Furthermore, a point is to be made that re-consenting health database and biobank participants for each emerging (secondary) research initiative may not only be impractical in a way that impedes research (thus, preventing public benefit), but also burdensome and inconvenient for participants.

The realization of the right to be forgotten[4]

Big data, and having one's personal health information included in a biobank or health database, in particular, may conflict with one's autonomy-based desire, or expectation, to control the disclosure of personal information and protect one's privacy. A biobank or health database participant may therefore, under certain conditions, invoke this newly emerging and increasingly recognized right to be anonymous, to be invisible. Such interest in (re-instating) anonymity may be realized through participants' right to revoke previously given consent to participate, by erasing their data, or removing their samples from the database or biobank. With research participation being voluntary, the *right to early withdrawal*, or *cessation of participation*, is a central tenet of medical research ethics. The participant must be informed at the point of entry to the biobank or health database, about this right. It must be made clear to participants that once they are withdrawn from the research their data and biological samples will no longer be accessible to researchers. However, data that have been aggregated, or data and samples that have already been used, cannot be withdrawn from ongoing or completed studies.

[4] Interchangeably termed "the right to erasure" (and in other contexts, "the right to a second chance").

Transparency

Given the power asymmetries inherent in the big data setting, particularly as reflected in issues surrounding consent and knowledge, transparency regarding usage goals and user identity on the part of data and sample controllers is imperative. Individual data subjects' right to receive information about data transfer and use—namely, whether data relating to them are processed, in what way, for which purpose, and by whom—is challenging for data controllers. As transparency represents accountability, it warrants such disclosure regarding the use of health data and biosamples. Data controllers are therefore obliged to relay or provide such information on their own initiative. Big data resources are prone to unanticipated third party (mis)uses. Such potential misuse lies at the intersection of transparency, privacy, autonomy (consent), and fairness (given that some organizations also use the data for profit but fail to return benefits to participants or the public).

Benefit sharing, equitable distributive justice

Secondary use of health data and human biological samples yields various potential benefits to participants (individuals or groups) and society as a whole. Health data and biosample users are morally obligated to return benefits or share profits derived from research to and with the public. Such return or sharing is accomplished by disseminating research-derived knowledge, sharing medical developments, implementing lessons learned, and improving health services for patients. Equitable distribution of the benefits generated by the secondary use of health data (that is, the fruits of research) among individuals or populations in the public is yet another challenge of the big health data endeavor.

Participation (via appropriate representation)

The public comprises genetically varied populations. A preliminary condition for the public's enjoyment of the fruits of scientific progress, namely, the benefits of research using health data and biosamples, is participation through appropriate representation in such databases and biorepositories. Such participation will render research outputs relevant and meaningful to all populations in a given society. Equality in the representation of individuals in the group whose data are included in the analysis should be assured as much as possible, in order to achieve more diverse genetic research. Each population group ought, therefore, to be given adequate representation in research, and exclusion of certain populations from research should be avoided.

Participation in health-related research, once perceived as a *burden*, has become an important protected *right*, and participation in biobanks is now considered by some a *moral duty* (echoing social solidarity), where the subsequent research using these resources is viewed as having the potential to benefit society at large and future generations. Such an (evolving) perception is consistent with the exponentially growing benefits (and recognition thereof) of having health information about individuals, ethnic/patient groups, and society as a whole, analyzed through secondary research. This is provided, of course, that beneficial research outcomes (results) are shared with, or returned to, data subjects, in some way.

Fair access

In the context of big health data (but not limited to this context), ensuring fair access to health databases and biosample repositories relies on two key conditions: *a)* (non-) exclusion of researchers; and *(b)* fair (reasonable/differential) access fees.

a) *(Non-) Exclusion of researchers*

Unjustifiably excluding researchers from access to health databases and biosources—for example, international research partners, nonprofit organizations, academics, and startup companies in their infancy —seeking to conduct secondary research, restricts access to these extremely valuable resources and ultimately narrows research opportunities with potential benefit to the public. Therefore, typically, exclusivity shall not be granted for the use of health data and biosamples, with the exception of data collected at the request of an external party, with funding or investment on its part. Such circumstances may be deemed justifiable exclusion, but even then, exclusivity shall usually be granted for as short a period as possible.

b) *Fair (reasonable/differential) access fees*

Health databases and biobanks sometimes apply, as a form of self-regulation, fee-for-access arrangements. Such arrangements may consequently hinder access to these valuable bioresources for some researchers, and they conflict with the principle of fairness in a way that may ultimately constrain academic freedom and prevent public benefit (for example, by hindering genomic discovery and obstructing the timely development of PM technologies). However, the interest of fair access must be balanced against proprietary interests of others (for example, data controllers), in a way that reflects the investment and costs of establishing and maintaining such data and

biorepositories. A fair fee-for-access policy may charge differential access fees for for-profit and non-profit research entities, that is, higher fees for organizations expected to derive financial benefit from use of the resource.

Guaranteeing access to health databases and biosources for researchers from diverse institutions and organizations by putting in place a fair (non-exclusive, differentially priced) access policy that does not unduly compromise access to such invaluable resources, is essential for keeping with the principle of fairness, in terms of access.

Discrimination and stigmatization

Health databases and biobanks may potentially contribute to research whose results are discriminating or stigmatizing for a particular community or social group. Research using such data or bioresources should be carried out in a manner that avoids discriminatory effects on individuals or communities, on the basis of racial or ethnic origin, genetic or health status, and sexual orientation.

Return of individual results and incidental findings to participants

Research using big health data inadvertently generates incidental findings (IF), that is, findings that are beyond the aims of the study, unintentionally discovered in the course of conducting research, concerning an individual research participant and bearing potential health or reproductive significance. Given the large scale of participants and the vast amount of data generated by next-generation sequencing technology, the conventional approach guiding biobank return-of-results policy was that returning individual research results and occasional IF to repository and data set participants is impracticable, ineffective, and overly burdening for researchers, to the point of hindering research. Consequently, the prevalent approach of biobanks and data sets was one applying a "no-return" policy. However, there is a growing consensus that researchers should at least offer participants individual IF of high clinical significance and actionability, where such findings are clinically urgent and where failing to return them might result in harm.

A policy supporting return of results and IF to participants, respects participants' autonomy (as participants have an inherent right to know personal health information so they can manage their own health risks). However, the current inability to correctly interpret certain IF and the (paternalistic) responsibility of researchers not to divulge unclear health information with limited (or no) meaning to participants, present a

challenge to the individual's right to personal health information. Furthermore, disclosure of results and IF could also cause unnecessary anxiety for participants and adversely affect their way of life and future plans. On the other hand, a non-return policy conflates a physician's and researcher's *duty to prevent harm* by disclosure of significant and potentially serious IF having clear benefit to identifiable individuals—i.e., findings indicating risk, which are medically actionable, for example, by means of preventive measures— with the autonomy-related individual *right not to know* certain (predictive) genetic information.

To avoid participants' erroneously attributing therapeutic intent, or prospects, to participation in big data research (also known as "therapeutic misconception"), researchers ought to make their (*non*)return policy (that is, whether such findings will be communicated) abundantly clear to participants within the consent process, at the point of entry to the database or biobank, thus allowing them to make an informed decision on participation.

Key bioethical considerations related to precision medicine

Most of the above depicted ethical considerations and challenges related to big health data and biosamples—the *sine qua non* resources for the development of personalized medicine—also apply equally (in)directly to the application of PM. Some of these considerations have a more specific, nuanced form when applied to PM, as will be shown below.

However, a few PM-specific ethical considerations have recently been developed. These pertain to the current status of PM—between bench and clinic. In the realization of PM benefits, several ethical challenges of *implementation science*[5] arise:

Evidence gaps

Establishing that a certain medical technology has reached its safe and mature stage is always a challenge. Typically, the available evidence to support a particular clinical innovation is inconclusive. The challenge is to determine when the evidence is sufficiently robust to warrant introduction of a PM technology into the clinic. The

[5] Implementation science is the scientific study of methods to promote the integration of research findings and evidence-based interventions into health-care practice and policy.

evaluation of the existing evidence shall take into account the estimated benefit, the nature and scope of potential harm, and the existence of alternative treatments.

Supporting clinical decision-making and patient-informed decision-making

Given the typical evidence gaps that are common in the introduction of novel technologies into clinical practice, clinicians need information to guide and support their professional decision-making regarding new PM technologies. Such information should address the strength of existing evidence supporting its use, potential harms, alternatives, the recognition that the best evidence available may have significant gaps, and potential results and follow-up recommendations. At the same time, patients must be educated regarding these issues so they can make informed choices regarding such novel treatments.

Acknowledging and redressing health-care disparities

The application of novel PM technologies is prone to exacerbating health-care disparities. Given that most genetic data and samples are habitually drawn from individuals of northern European descent (Caucasians) and with the prevalence of genetic variants varying across populations, the relative absence of non-Caucasians from health databases means absence from research and as a result, a poorer understanding of such differences as drug response and test results indicating a variant of unknown clinical significance (VOUS). Being under-researched entails deprivation of benefits from novel specifically tailored therapies. And so, as the potential benefits of PM scientific discoveries occasionally fail to reach (or are barely relevant to) patients who need them, including underrepresented groups of patients in genomic databases and biobanks is essential to enhance diversity. Such diversity is inherently pertinent to PM, which aims to individualize care by understanding differences in genetics. This, in turn, can promote the relevance of, and equitable access to, novel personalized therapies, thereby allowing patients to realize the (universal) right to enjoy the fruits of scientific advancements. Prioritizing research that addresses evidence gaps is therefore crucial for achieving more equitable benefits from PM.

Closing Remarks and Conclusions

Big health data is an essential ingredient in PM development. The wealth of health data is opening up novel possibilities for PM to achieve real breakthroughs in medical

discoveries. Maximizing the benefit of health information, through domestic and international scientific collaboration between data controllers (including health organizations and biobanks) and researchers, is therefore an important goal. However, an equally challenging mission, and a just, fair, and beneficial outcome of the secondary use of health data drawn from the public, is sharing the fruits of PM research with the public to increase its welfare.

But, clearly, for this enormous potential to be realized fully (or even moderately), a supportive data environment is essential.

In light of this review of the existing, as well as the unfolding, regulatory regime concerning secondary uses of big health data, it seems safe to say that the local data-sharing policy, with its emphasis on information security, consent, and research approval mechanisms, enables interoperability with external (both domestic and foreign) research organizations and health-care industry initiatives as well as with applicable international regulation.

As for the ethical issues associated with the use of big health data, and more specifically, with PM, these have been broadly, (in)directly addressed in the MoH recommendations for secondary uses of health information and the accompanying MoH circulars, mentioned in the regulatory section of this review. Both regulation-supporting and regulatory instruments have attempted to strike the appropriate balance between the increasing demand for access to big health data and exploitation of its hidden benefits, on the one hand, and the public's mixed interests (as a whole and as a large body of data subject individuals) in facilitating medical research and innovation, while maintaining patient privacy, medical confidentiality, and autonomy, on the other.

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