Intellectual Asset Management and Personalized Medicine: a bibliography of literature on public policy implications

What are the concerns for public policy raised by intellectual asset management in precision medicine innovation?

Sarah Ali-Khan PhD and E Richard Gold SJD
Centre for Intellectual Property Policy (CIPP), Faculty of Law, McGill University

Introduction

Policy makers and firms generally assume that intellectual property rights (IPRs) play an important role in enabling the translation of new technologies to patient care. For example, they see patents as key assets in attracting investment for the pharmaceutical and biotechnology industries by granting these companies a 20 year period in which they can exclude others from making, using, selling or importing what was invented. This limited term monopoly creates an incentive for innovation by giving inventors the opportunity to recoup the time and money invested in the research and development (R&D) process. This system relies on the hope that the public cost of this exclusionary period – which can lead to higher prices and the slowing down of other research and development– are more than compensated by the social benefit of the new good or service. For personalized medicine (PM, now more widely known as precision medicine, see: http://paceomics.org/index.php/outputs/policy-briefs/, Brief #10: Evolving Terminology: from Personalized to Precision Medicine) this means that the health benefits to patients or cost savings to the healthcare system make up for any adverse effects of the exclusivity. Despite these assumptions, there is little consistent empirical evidence concerning the benefits and costs of patents in the PM or other biomedical fields.

Despite the admirable policy goals of IPRs, they may act counter to innovation and societal good under some circumstances. Over the last almost 40 years, since patents were first granted for DNA sequences and other biotechnology inventions – the basis for many PM innovations – there has been sustained concern about the public policy implications of IP management in this realm. For example, patents applied to early stage discoveries or fundamental building blocks may block the free flow of genetic knowledge or research tools, and limit patient access to new diagnostics and medicines. Copyright, database rights and contractual agreements can complicate research progress. Privacy concerns and property rights over human tissues may restrict access to data and materials, and challenge public trust in the research endeavour. Further, the last two decades have seen several jurisdictions re-consider the patentability of genes, biomarkers, diagnostics and associated methods, unleashing uncertainty amongst PM developers and users. The diminishing market entry of innovative products, rising research costs and increasing pressure on healthcare systems for cost-effectiveness all contribute to a current push for new and creative approaches to IP. Insight on these questions may be informed by the rich discussion that has come before. However, the literature in this field occurs across a multitude of academic disciplines, publication types and grey literature, making it difficult to gain perspective on the issues at play.

Objective of this project:

The goal of this project was to:

1) Develop a comprehensive collection of relevant literature addressing intellectual asset management in PM innovation
2) Analyse the public policy and socio-ethical issues discussed and develop a taxonomy of key concerns
3) Organize the literature according to this taxonomy to provide a roadmap to the field for the use of students, academics, policy-makers and other PM stakeholders

To do this, we used a systematic search strategy (Arksey and O'Malley, 2005; Centre for Reviews and Dissemination, 2009; Moher et al, 2009) to identify all relevant academic, grey literature and policy documents across more than 60 academic disciplines and published by more than 90 non-profit, private, national and international organizations.

We then used qualitative thematic analysis techniques to identify the public policy and socio-ethical concerns discussed and develop a taxonomy of these issues (Ritchie and Spencer, 1994; Braun and Clarke, 2006).

Outputs:

We provide:

1) A downloadable bibliography of this dataset (330 documents published between June 2008 – June 2013), as a downloadable and editable excel file.
2) A guide organized by public policy themes, to aid in navigating this bibliography, and providing additional key information, as a word file.
   Both documents available: http://paceomics.org/index.php/outputs/tools-and-resources/.
3) A description of the systematic search strategy and thematic analysis underlying the dataset (this document)

Note that our full literature collection covers the years between 1980 – 2013. However, judging that the most recent 5 years would be of greatest immediate relevance to users, we prioritized analysis of these documents. We present documents from June 2008 to June 2013 in the accompanying bibliography. However, we describe the strategy used to develop the full collection below.

Methods

We employed a systematic and transparent method to identify all relevant policy and academic literature in the field. We primarily used the 'scoping review' methodology (Arksey and O'Malley, 2005, Paulden et al, 2015). However, a number of steps involved in a scoping review are the same as those of a systematic review, so we followed PRISMA and Centre for Reviews and Dissemination guidelines where relevant (Centre for Reviews and Dissemination, 2009; Moher et al, 2009). We then collected descriptive data from documents, and used qualitative thematic analysis techniques to identify the public policy issues raised by the management of intellectual assets in PM innovation discussed (Ritchie and Spencer, 1994; Braun and Clarke, 2006).

Scoping Review

Our document collection and analysis work consisted of six stages: 1) identifying the research question; 2) searching for relevant documents; 3) selecting documents; 4) indexing or 'coding' relevant material from documents; 5) refining and analysing the data and developing a taxonomy of the public policy or socio-ethical issues (and other themes); 6) grouping the issues under broad public policy themes and using these to annotate the bibliography representing the document dataset.

Identifying the research question

We developed our research question: "what are the public policy/socio-ethical and legal issues raised by the use of IPRs and related rights in the PM innovation pathway?" based on discussion within the PACEOMICS research team and our knowledge of the field.

Searching for relevant documents

Constructing the search strategy

We constructed a comprehensive search strategy supported by experienced Research Librarians within the McGill University Libraries network. We constructed the search strategy around three broad concepts: personalized medicine; intellectual property and innovation; and ethics and public policy. The field of PM has evolved over the last few decades, and terminology for PM has often changed names over this time (see PACEOMICS policy brief: see: http://paceomics.org/index.php/outputs/policy-briefs/, Brief #10: Evolving Terminology: from Personalized to Precision Medicine). To ensure that our literature search achieved comprehensive coverage, we first conducted a systematic search to identify all keywords, terms and synonyms for PM. This search strategy and the list of over 90 PM terms we identified is fully described at: http://paceomics.org/index.php/outputs/tools-and-resources/

Further, the term 'PM' only came into common usage around 2000 (Bates, 2009; Katnelson, 2013). To capture relevant literature prior to this time, we used more general search terms including 'biomarker', ' biotechnology', 'biotech drugs', 'genetic testing', 'pharmacogenomics', etc. To collect keywords, terms and synonyms for the concepts of intellectual property and innovation; and ethics and public policy, we used thesauri, discipline-specific encyclopedias, and information sciences controlled vocabularies including the National Library of Medicine's MeSH browser (see, http://www.nlm.nih.gov/mesh/MBrowser.html). See Appendix 1 for the referenced lists of all search terms for each concept. We constructed a comprehensive baseline search string using key terms selected from these lists (see Appendix 2, which shows this baseline search strategy which was used to search the SCOPUS database), that we customized according to the particulars of each database or electronic resource searched.

Search timeline

Our goal was to capture all relevant literature from the point that IPRs granted on human health biotechnology-related inventions became common-place, including DNA sequences, biomarkers, stem cells, genetically-modified entities, diagnostics and related methods, and research tools – all key technologies for innovation in PM. We chose 1980 as a start date for our collection, the year a landmark US Supreme Court ruling affirmed the patentability of genetically-modified living things (*Diamond v Chakrabarty*, 1980). This decision broadened the legal boundaries of patentable subject matter, leading to the granting of tens of thousands of patents on DNA sequences and other biotechnology inventions over the ensuing decades, and to extensive public policy concerns. We conducted our literature search between July 2013 and July 2014, and included documents published from January 1 1980 to June 30 2013.

Inclusion criteria

We aimed to collect all academic empirical studies, theoretical and opinion pieces, reviews, and grey literature policy documents and reports. We excluded all non-peer-reviewed material from academic publications including correspondence, news pieces, etc., book chapters, dissertations and conference proceedings, and other grey literature that was not policy or research. For reasons of practicality, we limited our collection to English language material.

Systematic literature search – academic literature

To capture documents across all relevant disciplines we searched sixteen electronic resources selected for their combined broad coverage across medicine, general sciences, economics, social sciences, law and ethics. These included SCOPUS, Pubmed, EMBASE, PAIS International, EthxWeb, Econolit, etc. (see Appendix 3 for the full list). Research Librarians in relevant disciplines assisted with database selection and in adapting our baseline search string as necessary. In a pilot phase, we extensively

tested our search strings to maximize their sensitivity and specificity in capturing target literature before embarking on the literature collection. See Appendix 2 for our baseline search string (used for the Scopus database, and then adapted for other databases as neccessary). See Appendix 3 for the full list of electronic resources searched, see Appendix 4 for search records.

Handsearches

We conducted hand searches of tables of contents for key relevant journals (Nature Biotechnology, Nature Reviews Genetics, Nature Genetics, Trends in Biotechnology, Genome Medicine,).

Law literature

We searched legal literature using the EBSCO or QuickLaw databases, using two Indexes to Legal Periodicals and Books: the full text and the retrospective indexes using our search strings as described above. If journals were not available through EBSCO, or better coverage was available through Quicklaw, we used the latter. We located journals that were not available in either of these manually via other databases available in the McGill libraries system.

We searched all Canadian law journals (31). However, given the large number of law publications recovered in our pilot study, we sought to increase our search specificity and ensure high-quality material. With this in mind we limited collection of publications from Australian, New Zealand, European law journals (17 journals) to those with impact factor (IF) >0.1, and for US journals to those with IF >1.0 (50 journals). We determined these cut-offs based on Washington & Lee (W&L) rankings (2005 – 2012). Journal IFs listed on W&L ranged from 0 - 3.29; they ranked 1644 journals in total, 758 of which had an IF >0.1 and 98 had an IF of >1.0. See:

http://lawlib.wlu.edu/LJ/indexOlderYears.aspx). We excluded obviously irrelevant journals from our search, for example *Journal of Air Law and Commerce*, and journals with no IF. To increase the coverage of our collection we also searched specialty law journals across economics, ethics, health, IP and science (144 journals).

Finally, to further limit our collection to high-quality material we excluded all articles authored by students and all articles designated 'Notes' (indicating student-authored material) from US journals. See Appendix 5 for the full list of law journals searched.

Three journals (Law and Development Review (US); Research in Law and Economics: a journal of policy (US); and Intellectual Property Quarterly (UK)) were not accessible through any database in the McGill Libraries system, so these were not searched. In total, we searched 240 law journals for this study.

Grey literature

We started by using the search engine 'Startpage' to identify grey literature using our search terms, and specifying the Google search limits for file type (PDF) and the website to be searched. We searched the websites of 57 relevant non-governmental, governmental and professional organizations' websites for relevant policy and research publications (list developed by S.A-K and R.G; see for the list of websites examined see Appendix 4). After we reviewed 1,199 records, our hit rate was 3%. Therefore, going forward we adopted a more efficient strategy; we hand searched the full texts of all the documents in the final study dataset published between 2008 and 2013, to identify all relevant policy and grey literature documents. We identified 24 documents using this approach (see Figure 1. Flow Diagram for Systematic Search Strategy).

Selecting study documents

We used our inclusion and exclusion criteria (as described above) to screen titles, abstracts and keywords of the hits recovered by our search strings, or if these were inconclusive or not available, the full text of the publications. To ensure retrieval of all relevant documents, three research assistants completed a training in which they reviewed two sets of 150 documents (300 in total). After training, the average pairwise agreement with the research leader (SA-K) was 87.2% (Cohen's Kappa, calculated using Re-Cal software, available at: http://dfreelon.org/utils/recalfront/). Further, over the course of the screening process, we held weekly research meetings to review document inclusion/exclusion and gain consensus on any discrepancies.

Our searches resulted in 18,289 hits (see Figure 1: Flow Diagram for Systematic Search Strategy). We retrieved the full-text of all academic and grey literature documents that discussed public policy and socio-ethical issues raised by intellectual asset management (including IPRs and related rights (such as database rights) and knowledge management strategies more generally) in PM innovation. We excluded all documents discussing biotechnology or genetics not related to human health. Notably, we did retrieve documents discussing biotechnology manipulation of animals, plants and microorganisms if directly applicable to human health (for example, transgenic plants to express recombinant medicines). We excluded 16,050 records. We deleted 505 double citations. We then downloaded the citations and full-texts of all remaining potentially relevant documents (1,994, published between 1980 – 2013) to an Endnote reference management database (X6.0.2, Thomson Reuters 2012). At this point we limited the dataset to publications from June 2008 – June 2013, thus leaving 824 documents for full-text review.

Data collection and analysis

We conducted data collection and thematic analysis in two phases. In the first, the retrieved study documents were distributed amongst the 12 research assistants and the

research leader (SA-K). They read the full texts, excluded those that fell outside of the inclusion criteria, collected descriptive data and carried out thematic analysis as described below (June 2014 to Nov 2015). In the second phase, the research leader reviewed the entire dataset to ensure the accuracy, consistency and internal validity of the thematic and descriptive data (Jan – Apr 2016).

Descriptive data collection

We also collected descriptive data on each document. In addition to standard bibliographic data (title, authors, date of publication, journal or publishing body, etc.), we recorded: the primary academic discipline of the first author if relevant, the primary

institution or organization to which they were affiliated and the country of this institution. We noted if the publication was academic or grey literature, and assigned it to one of the following categories based on its features and content, and considering the publication type assigned by the journal in question, if relevant. *1) Editorial:* all journal editorials; *2) Empirical – qualitative:* all qualitative research including case and interview-based studies, and publications whose content drew largely on such data; *3) Empirical – quantitative:* all quantitative research studies including surveys, quantitative analyses of patents, etc.; *4) Literature review:* all documents whose authors identified the work as a literature review. Note that these were not always reported in classical research article format, but they specified or referenced the methodology used to generate the literature collection; 5) *Meeting report:* all reports from a meeting or workshop; *6) Opinion/thought:* pieces often, but not always, appearing in 'opinion', 'commentary', 'policy forum', 'open debate' sections of journals. They all advocated a particular position or viewpoint; *7) Project-specific report:* these presented policy outcomes, lessons learned or observations from specific projects, for example the Biomarkers Consortium or the Wellcome Trust Sanger Institute data sharing policy; *8) Policy:* all grey literature policy documents – i.e. policy documents published outside of academic publishing

channels; *9) Report:* all grey literature research reports – i.e. research reports published outside of academic publishing channels; *10) Review:* all general reviews. These were differentiated from literature reviews as described above, by the fact that authors did not identify them as formal literature reviews and did not specify methodology. Often these publications appeared in 'review' journals or in 'review' sections of a journal; *11) Theoretical:* these publications analyzed conceptual, historical or philosophical understandings related to personalized medicine itself or intellectual property law. Many of these were penned by authors whose academic discipline was law, or who were affiliated with law firms.

Thematic data analysis

The thematic analysis process consists of 7 key phases:
(1) familiarization with the research material; (2) generation of an initial analytical coding framework and application to the dataset — researchers identify passages of text relating to a common theme or idea relevant to the research question and index them with corresponding 'codes'; (3) searching for and verification of codes across the entire dataset; (4) identification of relationships between codes and of distinct differences between subgroups of ideas; (5) definition and naming of themes encompassing groups of codes; (6) re-reading of a sample of the texts and verifying codes based on emerging themes; and finally (7) mapping and interpretation of the overall taxonomy of themes identified from the data. These 7 steps were carried out as an iterative process.

Before analysis began, the research leader developed an *a priori* codebook based on reading a random subset (50) of the dataset documents and knowledge of the field (steps 1 and 2 above). This codebook laid out the analytical coding framework, including the names of analytical categories, definitions for assigning these categories to text and examples. Prior to starting the indexing process, the coders completed a week-long

training session, applying the coding framework to five sets of six dataset documents guided by the codebook. This process continued the group determined that all conceptual issues were resolved and that all coders were clear on how the coding framework should be applied. During the analysis process, coders employed a 'constant comparison' methodology, whereby they systematically compared emerging analytical categories with the codebook categories. We held weekly meetings of the entire research team, in which we refined and augmented analytical categories, updated the codebook, recorded analytical insights and built a preliminary taxonomy of the data. These processes were documented and organized using NVivo 10 qualitative analysis software (QSR International, 2012. www.qsrinternational.com). All excluded documents were reviewed by at least three team members including the research leader.

Data verification and constructing the taxonomy of public policy issues

When all relevant data from the documents was indexed, the research leader and two research assistants completed the refining and thematic analysis of the indexed text (steps 3 – 7 above). This involved re-reading all the indexed text in detail, and comparing, sifting and sorting the codes according to the key aspects or concepts discussed. This process culminated in mapping the themes and sub-themes of public policy issues to create a taxonomy that reflects the relationships between them. The research leader then reviewed the entire dataset to ensure accuracy, consistency and internal validity.

Search results

The PRISMA format diagram (Fig 1) shows the four steps of our systematic search process. Our search strategy identified 18289 records, of which we excluded 16050 according to the exclusion criteria. We further identified 265 documents through hand searches of journals and of the now defunct IPGen database (a component of the HumGen database series until early 2013, see: http://www.humgen.org). We

downloaded the citations and full-texts of the remaining 2504 documents to our Endnote database, at which point we removed a further 505 duplicates. The high number of duplicates is one indication of the comprehensiveness of our search. Often, the same document was recovered from several different sources. We were unable to locate PDFs for 5 documents. We then restricted the dataset to only those documents published from Jan 1 2008 to June 30 2013. On full-text examination of the remaining 824 documents, we further excluded 518 according the criteria noted above. We identified 24 relevant policy or grey literature reports referenced in the dataset documents and retrieved these. After this assessment process, we retained a final dataset of 330 documents for analysis.

Thematic classification of study documents

Our analysis identified 98 categories and multiple sub-categories of public policy, socio-ethical and legal issues raised by intellectual asset management in the field of PM innovation. For the purposes of this bibliography, we assigned a broad theme to each of the 330 study documents based on the main focus of the public policy and socio-ethical issues discussed in each one. We note the number of documents in each thematic category in brackets beside the titles below. An annotated guide to the documents is available: X and the full bibliographic details can be downloaded as an excel file here: The broad themes capturing the public policy and socio-ethical issues discussed in our document collection are:

Alternatives to traditional patents (3): These publications propose alternative kinds of patents that may be better calibrated for use in personalized medicine, biotechnology and genomics innovation. The patent types described may address legal and socio-ethical concerns raised by the use of conventional patents in these domains.

Enabling access to patented research tools (5): These publications discuss concerns about diminished access raised by the patenting of 'research tools', and propose

solutions to address these issues, other than alternative types of patents (contained in the theme above). This category includes all publications whose explicit focus was research tools.

Impact of intellectual property rights and business models on research and innovation (38): These publications examine the impact of intellectual property rights, licensing and business models on research and innovation in health biotechnology. Topics discussed include the potential for creation of an anti-commons, patent thickets and blocking, and conversely the role of patents in incentivizing innovation.

*Intellectual property rights, business models, and access to health care (41): T*hese publications address ways in which intellectual property rights on health biotechnology affect access to healthcare. This category includes many case studies exploring the impact of licensing and business models on patient access to genetic diagnostics.

Open Science, data-sharing or collaboration (105): These publications discuss open science, collaboration, partnerships, and data-sharing. Aspects include why these initiatives are relevant, challenges to their implementation, and opportunities and solutions they offer. Many of these documents are presented as project-specific reports and policy papers.

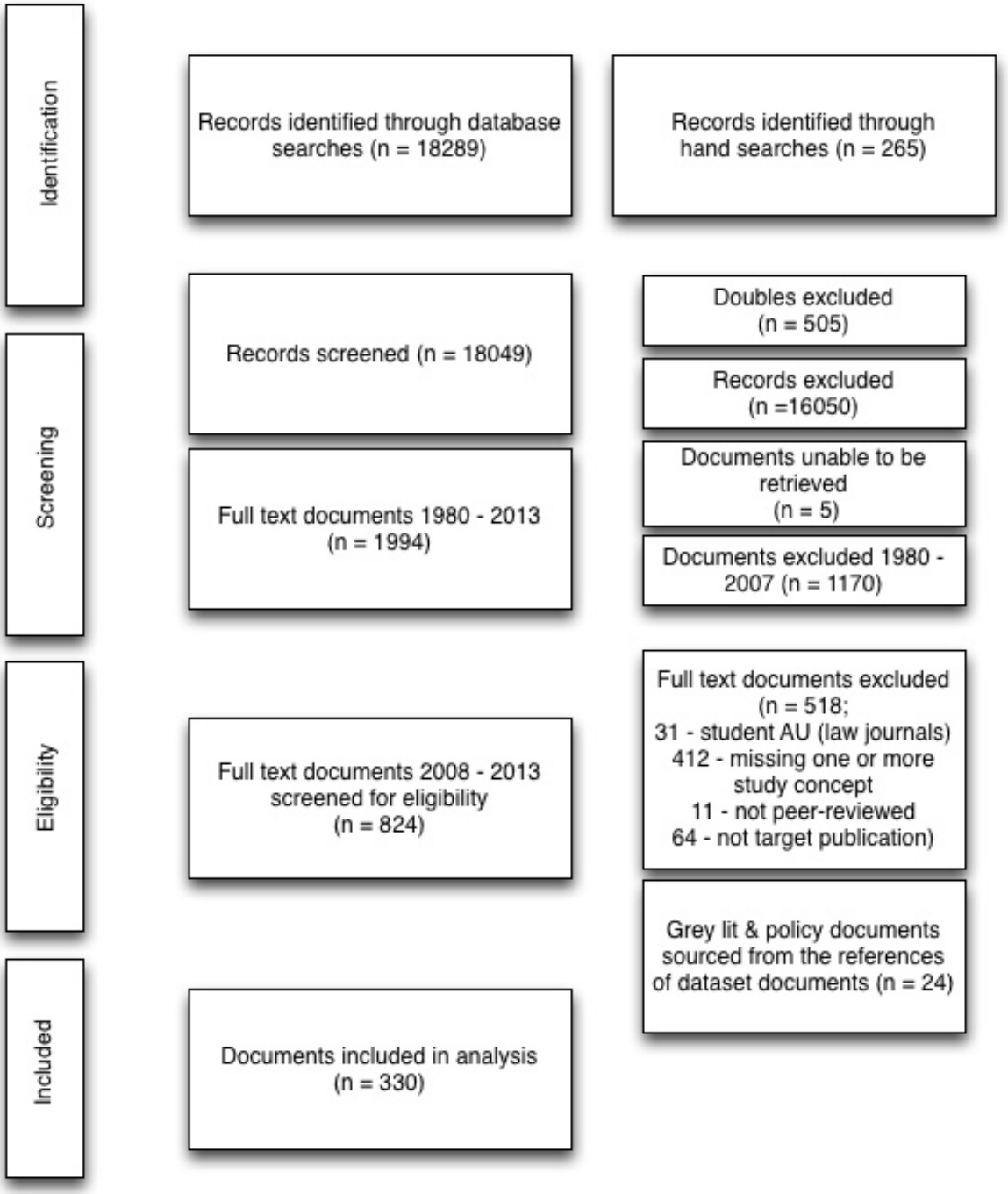
Ownership, informed consent and benefit-sharing (32):

These publications discuss issues around ownership, commercialization, informed consent, and benefit-sharing related to research on human biological materials and data. Some documents address these issues specifically in the context of biobanks.

Patentability of biotechnology invention (78): These publications discuss the patentability of health biotechnology innovations, including DNA-based inventions, whole genomes, chimeras, stem cells, etc. Many are theoretical articles by law scholars, which dissect statute and case law relating to patentable subject matter, and novelty, non-obviousness, and utility standards. .

Patents and race (3): These publications explore how patenting (and subsequent

Figure 1: Flow Diagram for Systematic Search Strategy



marketing) of some personalized medicine innovations may propagate racialized thinking in society. In particular, the case of the heart failure drug BiDil, which was patented for use in African American patients, is discussed.

Religious views on commercialization (1): These publications discuss the socio-ethical concerns raised by patenting and commercialization of health biotechnology inventions from a religious perspective.

Role of intellectual property rights in health biotechnology and personalized medicine innovation in developing countries (10): These publications discuss the challenges and opportunities presented by intellectual property systems with respect to health biotechnology and personalized medicine innovation in developing countries.

Social determinants of innovation (4): These publications explore the impact of social forces on research and innovation pathways.

The role of technology transfer offices in facilitating innovation and access (5): These publications discuss technology transfer offices at universities and academic research institutions, and the positive and negative aspects of their role in facilitating innovation and access.

Next steps:

We are now in the process of using statistical approaches to explore the relationships and patterns in the thematic and descriptive data we have collected.

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