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Comparing different scientific approaches to personalized medicine: research ethics and privacy protection

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Abstract

In this article, two different scientific approaches to personalized medicine are compared. Biorepository at Vanderbilt University (BioVU) is a genomic biorepository at Vanderbilt University Medical Center in Nashville, TN, USA. Genetic biosamples are collected from leftover clinical blood samples; medical information is derived from an electronic medical records. Greifswald Approach to Individualized Medicine is a research resource at the University of Greifswald, Germany, comprised of clinical records combined with biosamples collected for research. We demonstrate that although both approaches are based on the collection of clinical data and biosamples, different legal milieus present in the USA and Germany as well as slight differences in scientific goals have led to different 'ethical designs'. While BioVU can successfully operate with an 'opt-out' mechanism, an informed consent-based 'opt-in' model is indispensable to allow GANI_MED to reach its scientific goals.

Keywords

biorepositories; personalized medicine; research ethics; research regulation

Applied genetic research has answered numerous questions concerning the factors that contribute to the inheritance, causation and severity of human diseases. While earlier phases of research have tended to concentrate on straightforward genetic inheritance and causation, advances in laboratory science and technology have led to a shift in focus within the field of genetic research to more complex systems. Recent research centers its attention on the

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interaction of genetic disposition and environmental factors in the causation of disease, and the use of biomarkers to identify and guide therapy for these diseases.

Biomarkers are substances that can be detected in biosamples, such as blood or urine, that facilitate diagnosis of diseases or enable personalized treatment planning, tailoring and monitoring of therapy regimens. Biomarkers, which can be genomic, epigenetic or proteomic in nature, are seen as an important resource for an emerging approach to medical treatment, personalized medicine. This approach has been hailed as an advancement that will bring about a new era in medicine [1,2].

Despite the enthusiasm that has grown up around this field, personalized medicine, both as a research topic and as an approach to medical care, is not yet based on a set of specific and well-defined methods and concepts [3]. The various approaches have in common the goal of developing new pathways and therapy strategies that are better adapted to each patient's individual physiology, thus making medical care more effective and efficient. One dominant view of personalized medicine anticipates that medical treatment will be improved by using the knowledge about physiological risks and genetic predispositions to customize therapeutic strategies and diagnostic evaluation. Since the detection and measurement of biomarkers will be the key to this approach, much of the current research in the area of personalized medicine focuses on the identification and measurement of biomarkers that identify or determine risk.

One of the challenges for developing a scientific basis for personalized medicine is the statistical consideration that arises when a large number of variables need to be considered. Technically speaking, approaches to personalized medicine are not focused on tailored treatments that are optimal for an individual patient. Rather, personalized medicine is an approach to medical care that accounts for a larger set of variables than used in the past. Patients with a single disease are stratified according to sociodemographic groupings, biomarker results, genetic test results and potentially many other factors. For this reason, some prefer to speak of stratified medicine rather than personalized medicine [4]. In order to detect any single factor responsible for a small effect among a large number of parameters, large samples sizes are required.

Over the past decade, very large biorepositories and clinical databases have cropped up around the world. These large collections of bio-samples and medical record information are the innovative answer to the problem of generating very large, but also very expensive, sample sets for the elucidation of complex systems. Methods for planning and designing these biorepositories and corresponding databases are not yet standardized, and different approaches have been taken throughout the world. In some countries, like the UK, a large-scale population-based repository has been developed [101]. In other countries, like the USA and Germany, research and healthcare institutions have led the way.

These differences occur within different national contexts that constrain and shape decisions about how to proceed. Public regard for government-organized research is certainly an important factor in some countries [5]. In addition, federal and local policies that regulate research and privacy standards determine which models for biorepositories and databases are permissible. These factors influence decisions about informed consent, sample collection, data management, governance and many others.

In this article, we will compare and contrast the regulatory frameworks that have shaped the development of biorepositories in the USA and Germany. This comparison is important for at least two reasons:

- The institutional model for the development of biomarker-related research is similar in these two countries.
- The different regulatory frameworks in the two countries render certain models permissible in one country, but not in the other. As a result, different strategies for obtaining informed consent have to be established.

In order to ground this discussion on real-life examples, we will compare the efforts that have been undertaken at our local institutions, Vanderbilt University (TN, USA) and Ernst-Moritz-Arndt University Greifswald (Germany), to establish and operate biorepositories and the corresponding databases.

Vanderbilt University Medical Center in Nashville, has developed a biorepository (BioVu) based on leftover blood from clinical samples. Samples are obtained without formal informed consent, although patients are given the opportunity to opt out of this research. The Greifswald Approach to Individualized Medicine project (GANI_MED) at the Ernst-Moritz-Arndt University in Greifswald focuses on enabling biomarker research by developing a biobank comprised of biological samples and medical record information collected through routine clinical care from special hospital wards, such as cardiology, neurology and internal medicine.

BioVU

Legal & ethical basis

US federal policy regulates the conduct of research on human subjects. The Common Rule separates research into two categories: human subjects research, and nonhuman subjects research. A human subject is defined in the policy as a "living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (5 CFR, Part 46, Section 102)" [6]. On the basis of this definition, research either involves human subjects, and is thus directly regulated under this policy, or it does not, and is thus not subject to direct regulation. Human subjects research involves a number of research requirements, including review by a research review board, ongoing monitoring of research activities, and the requirement that all potential research subjects be provided information before agreeing to participate.

Research institutions are required to maintain institutional review boards that review and monitor human subjects research to ensure that it is conducted in compliance with the law. Compliance includes such elements as training of researchers on the responsible conduct of research, informed consent and reporting of adverse events. The government agency that oversees compliance, the Office of Human Research Protections (OHRP), develops and publishes guidance documents that interpret the Common Rule and clarify how its provisions will be enforced.

In 2004, the OHRP published guidance clarifying its interpretation of the Common Rule as it applies to repositories comprised of de-identified samples. In this guidance, OHRP concluded that repositories including only information that is identified by a code and not by personal identifiers is not classified as human subjects research. This is because the policy defines a human subject as a person whose "identifiable private information" has been obtained [7].

This OHRP guideline provides the basis for BioVU, wherein only de-identified samples are stored. BioVU is a biorepository derived from electronic medical records and leftover blood samples. Electronic medical records are de-identified through an informatics process that

'scrubs' documents of personally identifiable information. It is able to relate documents within a medical record to one another through the use of an encrypted code. Samples are obtained from blood leftover after clinical testing. They are connected to the associated medical record using the same encrypted code [8].

Under the OHRP definition, this biobank does not qualify as human subjects research. It is therefore subject to a different set of rules. Requirements for human subjects research, such as review by the institutional review board and informed consent of potential participants, is not required under the Common Rule or the OHRP's interpretation of that policy.

Even though the Common Rule does not directly regulate nonhuman subjects research, BioVU includes extensive review and oversight that exceeds the bare requirements of the policy. This is for two reasons: the indirect influence of the policy, and the ethical considerations on which the Common Rule is based.

Indirect influence of policy

Nonhuman subjects research is often said to be 'unregulated' because the provisions of the Common Rule do not directly apply to this category of research. However, research on de-identified human samples obtained without interaction by the researcher can only remain in the category of nonhuman subjects research if no intentional or routine identification occurs. That is, as soon as re-identification occurs, this research immediately shifts from the nonhuman subjects research category to the human subjects research category. This shift in category can easily place a research project into noncompliance with the Common Rule if it is not already following the requirements for human subjects research, including, for example, informed consent. We call this category of nonhuman subjects research that includes human samples and is therefore at risk for shifting into the human subjects category "human nonsubjects research" [9].

Therefore, even though it is considered unregulated, human nonsubjects research can only remain in compliance with federal policy if it either: very closely guards against re-identification; or adheres to all requirements for human subjects research.

Goals of research

If the regulatory and ethical environment of the USA provides the context for which types of biorepositories are possible, the goals of the investigators determine which of the possible designs will be pursued. In the case of BioVU, the primary focus has been on identifying links in both directions between phenotypes and genotypes, utilizing such methods as genome-wide association studies (GWAS) and the reverse method called a phenome-wide association study (PheWAS) [10,11]. Some types of research are not possible using this model. For example, because dates and geographic locations are potentially identifying, they are scrubbed from the de-identified copy of the electronic medical record. This makes research looking at events that happen at particular times (epidemics) or places (environmental exposures) impossible. Also, because patients have not given explicit informed consent for studies, research addressing potentially controversial or socially contested issues is not permitted by the biorepository.

The types of research that are possible critically require translating a complex medical record into phenotypes that can be identified electronically as present in some patients (cases), and confirmed with some certainty to not be present in other patients (controls). Depending on the definition being used for a particular phenotype, the identification of cases can be a straightforward process; the mention of a diagnosis or medication over several patient encounters provides a significant amount of information. On the other hand, the identification of controls can be quite difficult. In order for a patient to be classified as a

control, enough data must be available to confirm that the patient does not have a condition. Patients who receive care within the institution on only one occasion or for only a single medical problem might easily have a condition that does not get recorded because it is irrelevant to the visit. Longitudinal data is thus a necessary prerequisite to classify a patient as a control.

Longitudinal data can be added to the de-identified research record through the use of the encrypted research code. New documents that are entered into the electronic medical record can be linked with existing documents in the de-identified research record and with stored DNA obtained from leftover blood. Recontact by investigators is not necessary for this approach to obtaining longitudinal data prospectively.

Because BioVU includes information from the electronic medical records, reports stored there are also available in de-identified research records. Laboratory results obtained by providers for patient care are included in the research records. Text reports from radiographic studies and pathology evaluations are also available in the de-identified research records. However, radiographs and other images, including scanned documents, patient photographs and outside medical records, are not included in the de-identified research record, since there is not currently an effective method to scrub identifiable information from such images.

Research ethics considerations

The biorepository model adopted in the design of BioVU had no precedent when it was being planned. Early exploratory work by the investigators who started BioVU revealed that lay people seemed to approve of BioVU, but they expressed a desire to have a choice about whether their sample would be included [8,12].

More recently, quantitative population-based research we have conducted in our local region (Nashville, TN, USA) has demonstrated that general support for this genomic biobank is very high, 93.9%, as long as investigators give patients the opportunity to opt-out. When asked if they would support a biobank that is conducted without getting the written permission of participants, we found much less support, only 45.5% [13].

This finding in public opinion is consistent with the ethical principles that are summarized in the Belmont Report and form the basis for the US human research protections policy [14]. This policy is based on the principle that persons should have the ability to determine for themselves what will be done to their bodies or samples removed from their bodies (autonomy). Going further, persons not only have a right to decide for themselves, but also a right to be treated with respect by researchers and research institutions. It is not surprising that potential research participants want to give their consent for their samples to be used; this value is central to the policies that regulate human research in the US.

Since its inception, BioVU has operated on the basis of an opt-out model. When patients are presented with standard consent forms upon checking into clinics for routine visits, one of the forms includes a large checkbox next to the statement “Do not use my leftover blood for the DNA databank” [15]. Patients who check this box are flagged in Vanderbilt’s electronic medical record system as having opted-out from inclusion in the DNA databank. Thereafter, their sample will never be used again for research, even if they do not check the box on their next clinic visit.

To be clear, there are no regulations that require an opt-out from research. This is the result of guidance from well-established principles of research ethics [15]. These principles are so

well established that patients expect them to be followed. Of note, however, the opt-out model has not yet been adopted at other institutional biorepositories in the USA.

GANI_MED

Legal basis

While a number of laws and legal guidelines regulate aspects of GANI_MED, three components of the German law are of particular importance: the national and local laws of data protection (Bundesdatenschutzgesetz, Datenschutzgesetz der Länder), the criminal law (Strafgesetzbuch) and the civil law (Bürgerliches Gesetzbuch). According to the criminal code, every patient must be able to exercise the right of self-determination with respect to his or her body, since every nonauthorized invasive procedure is a bodily injury and could be prosecuted. Once biosamples are collected, the civil law regulates the right of ownership over these samples. At first, the patient is the owner of this material. This ownership is transferred to University Hospital Greifswald, though, when the material is deposited as a part of the GANI_MED project.

According to national law (Bundesdatenschutzgesetz) as well as local laws (Datenschutzgesetz der Länder) encoded data that can be re-identified is personal data, and such data cannot be used without the consent of the donating person [16-18]. Because of these laws permission must be obtained from patients whenever personal data will be used for research purposes. After consent is given, though, the law continues to regulate how data may be used. For example, during the research process data must not be able to be associated with the donating persons [102]. This raises problems if a client must be contacted. Re-identification must therefore be managed by a completely autonomous trustee institution.

An important contrast between US and German laws becomes apparent at this point. Under US human research regulations data that is de-identified can be collected without the explicit consent of the donating person, even if it is not completely anonymized. By contrast, the use of de-identified but re-identifiable data without consent is not allowed according to German law [17-19].

Goals of research

Greifswald Approach to Individualized Medicine is designed to enable multidimensional research oriented toward identification and validation of biomarkers for specific human diseases, which includes the study of the proteome, the transcriptome, the metabolome and the genome. In order for GANI_MED to reach these scientific goals, biosamples and health-related information are collected in a biorepository and supporting database. Longitudinal data is gathered from clinical records and through recontact with patients and providers, which enables the long-term monitoring of the clinical course of diseases, including morbidity and mortality.

Medical information is collected mainly through routine clinical care in accordance with research quality standards. Additional evaluations that are not clinically indicated, such as MRI examinations, are performed to supplement research records. The treatment contract between the hospital and the patients does not cover research evaluations that are not part of routine clinical care, including the collection and analysis of biosamples. As a consequence, every patient needs to be asked explicitly for his or her permission during the GANI_MED informed consent process [17].

An auxiliary aim of the GANI_MED project is to improve the quality of clinical care provided to patients. Every clinical process that will generate information to be included in

GANI_MED will be modified to reconcile both the practical needs of clinical routines and the scientific aims of the research. Clinical assessments will be improved using highly standardized methods for data collection in accordance with standard operation procedures that will be developed specifically for GANI_MED and comply with scientific quality criteria. This includes comprehensive training and certification procedures for all observers. In addition, regular monitoring of the collected data, including analyses of intra- and inter-observer variability, will confirm that strict quality criteria are fulfilled.

Likewise, the data generated will be available for answering both clinical and research questions. Over time the clinical utility of some of the biomarkers under study will be validated. Because patients' laboratory results will be available to clinicians, they will have the opportunity to personalize the evaluation, diagnosis and treatment of the participating patients without needing to obtain additional testing.

In order to make these improvements in personalized medicine sustainable, they will need to be proven not only feasible but also economical. The main question is: what costs are connected to this approach? To obtain this information an economical analysis will be conducted throughout the data collection process utilizing cost reports from health insurance companies and participating providers.

Ethical decisions: the informed consent process for GANI_MED

Due to the fact that GANI_MED will involve follow-up studies and health monitoring, recontact is an important aspect of the GANI_MED concept. Identified personal data is needed to recontact patients, so explicit informed consent is indispensible; this requirement would apply in either Germany or the USA.

The informed consent procedure adopted by GANI_MED presents participants with choices in a simplified, modular format.

In the first module of the consent form, the patient is asked to agree to the use of his or her clinical data for scientific uses. If the study design anticipates the use of examinations that will be conducted for scientific rather than clinical or diagnostic reasons, the patient's agreement to such special procedures is requested. While incidental findings from diagnostic procedures will be handled according to standards of care, patients are asked whether they would like to be provided with the results of examinations conducted for scientific aims [19-21]. In this way, the 'right not to know' is protected.

In the second module, patients are asked for their permission to both store biosamples such as blood, urine and biopsy tissue and to analyze these samples scientifically. Again a 'right not to know' with respect to the findings generated in the analysis of biosamples is offered [21].

In the third module, permission is requested to contact the patient again at a later time.

The declaration of consent ends with an explanation of a patient's right to change his or her mind and to countermand the participation in GANI_MED at any point in time.

On a separate document (called the 'Authorization Form') the clients are asked for their authorization to contact their general practitioner, their health insurance company and the population register to obtain information concerning the patients' illnesses and related treatment costs, and changes in residence or vital statistics.

The entire informed consent process is accompanied by an informational document explaining each element of the informed consent in detail.

The consent forms are computerized and the patients' signature is automatically scanned and digitized. Patient preferences from these modules are stored in the central database and called by the system whenever a consent-sensitive process is triggered.

Discussion

Although different approaches were chosen in Nashville (USA) and Greifswald (Germany), the research is dedicated to very similar goals. Both GANI_MED and BioVU were established to develop the knowledge and techniques necessary to realize the potential of personalized medicine (Table 1). Both are designed to enable a wide range of research through the establishment of a large-scale biorepository comprised of biosamples and medical record information. BioVU uses leftover blood samples from the clinic and gathers data generated through routine clinical care. Efforts to implement personalized medicine based on standardized clinical procedures are conducted independently from the research effort. BioVU is therefore a resource reflecting as-is clinical care, and research that is generated therefore reflects real world clinical practice rather than artificial scenarios designed to attain research goals. Owing to the connection between the identified medical record and the de-identified medical record, research records can be supplemented and updated over time. This ability allows BioVU to serve as a prospective, longitudinal research resource without the requirement for recontacting patients.

GANI_MED collects materials and data from patients who are affirmatively donating them. Standardized protocols are embedded within the clinical routine, which will help to minimize the need for sophisticated postprocessing of data. Follow-up studies are planned to supplement initial assessments with longitudinal data. For this reason, selected patients will need to be re-identified and recontacted.

As shown above an important difference between the designs of BioVU and GANI_MED is the degree to which the clinical routine is altered. While the clinical routine is not modified to serve the aims of BioVU, GANI_MED seeks to adapt elements of the clinical workflow to improve data quality of diagnostic information and documentation for scientific use. This will be attained through the standardization of critical clinical processes and examinations as well as through regular data monitoring.

BioVU and GANI_MED have adopted different approaches not only because of slightly different research goals, but also because of the differing legal milieus of the US and Germany. These differences are most apparent in the areas of the security of personal data and regulations governing human research. US regulations, particularly the guidelines of the Office of Human Research Protections, have enabled BioVU to adopt an opt-out approach intended to improve the efficiency of sample collection while preserving patients' right to make autonomous decisions regarding the use of their biosamples. This approach provides economic benefits, since expenses associated with patient recruitment and consent are reduced. In addition, participation bias is likely to be minimal in studies based on this biorepository, since the opt-out rate has been low [15].

By contrast, German regulatory requirements for an explicit informed consent process preclude the use of an opt-out model in this country. GANI_MED is still capable of efficiently gathering clinical data, and its model has the advantage of supplementing clinical data through research-specific evaluations. Both the clinical and research-specific data can be collected longitudinally, allowing for a prospective epidemiologic approach with patients who have agreed to be recontacted. Both the informed consent process and recontact of patients requires resources, but the potential scientific utility of the information that is gathered using this approach justifies the added expense. As a number of studies have

shown, opt-out methods generally lead to higher participation rates compared with opt-in methods [22,23]. For this reason, participation bias may be more prominent in opt-in research studies [22]. Despite these trends, high participation rates and careful analytic methods can serve to mitigate the impact of participation bias.

Future perspective & conclusion

BioVU and GANI_MED are examples of biorepository-based scientific approaches to personalized medicine that have been designed to pursue a specific set of research goals within specific regulatory frameworks. In the next 5–10 years, approaches to biorepository design will be further developed in order to meet the evolving goals of personalized medicine. Multiple biorepositories have already engaged in data-sharing agreements and consortia in order to answer scientific questions that require exceptionally large datasets. This practice will likely become even more important as scientists move from the scientific 'low-hanging fruit' into more complex questions relating to personalized medicine. Different regulatory milieus of the constituent biorepositories will continue to inform the direction and variety of innovation in this area, and in particular as consortia continue to cross international boundaries. For this reason, work to characterize and compare the country-specific legal frameworks for scientific approaches like BioVU and GANI_MED will continue to grow in importance.

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Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1. Golubnitschaja, O. Predictive Diagnostics and Personalized Treatment: dream or reality. Golubnitschaja, O., editor. Nova Biomedical Books; NY, USA: 2009.

2▪. Niederlag, W.; Lemke, H.; Golubnitschaja, O.; Rienhoff, O. Personalisierte Medizin. Vol. 14. Health Academy, Wissenschaftliche Buchreihe zur Hochtechnologiemedizin; Dresden, Germany: 2010. Provides insights into personalized medicine from a multidisciplinary perspective

3▪. Hüsing, B.; Hartig, J.; Bührlen, B.; Reiß, T.; Gaisser, S. Individualisierte Medizin und Gesundheitssystem. Vol. 126. Büro für Technikfolgen-abschätzung beim deutschen Bundestag Arbeitsbericht; 2008. Classifies and analyzes the different varieties of personalized medicine

4. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. 2007; 6(4):287–293. [PubMed: 17380152]

5. Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Genetic research and donation of tissue samples to biobanks. What do potential sample donors in the Swedish general public think? Eur J Public Health. 2006; 16(4):433–440. [PubMed: 16207726]

6. Federal Register: 45 CFR §46.102(f) Definitions

7. Office for Human Research Protection: Guidance on research involving coded private information or biological specimens. Department of Health and Human Services 45 CFR part 46. 2004

8▪. Roden DM, Pulley JM, Basford MA, et al. Development of a large-scale de-identified DNA biobank to enable personalized medicine. Clin Pharmacol Ther. 2008; 84(3):362–369. Discusses a wide range of issues that arise in the development of a human nonsubjects biorepository. [PubMed: 18500243]

9. Brothers KB, Clayton EW. 'Human non-subjects research': privacy and compliance. Am J Bioeth. 2010; 10(9):15–17. [PubMed: 20818548]

10▪. Denny JC, Ritchie MD, Basford MA, et al. PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene–disease associations. Bioinformatics. 2010; 26(9):1205–1210. Proposes a novel and highly promising approach to genomics made possible through biorepositories based on medical records. [PubMed: 20335276]

11. Ritchie MD, Denny JC, Crawford DC, et al. Robust replication of genotype-phenotype associations across multiple diseases in an electronic medical record. Am J Hum Genet. 2010; 86(4):560–572. [PubMed: 20362271]

12. Pulley JM, Brace MM, Bernard GR, Masys DR. Attitudes and perceptions of patients towards methods of establishing a DNA biobank. Cell Tissue Bank. 2008; 9(1):55–65. [PubMed: 17960495]

13. Brothers, KB.; Clayton, EW.; Morrison, DR.; Pulley, JM.; Masys, DR. Acceptability of an opt-out pediatric biobank based on electronic medical record and residual blood samples. Presented at: Pediatric Academic Societies; Vancouver, British Columbia, Canada. 1-4 May 2010;

14▪▪. Ryan, KJ.; Brady, JV.; Cooke, RE., et al. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. US Department of Health, Education, and Welfare; Washington, DC, USA: 1979. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The definitive statement on the concepts underlying human subjects protections in the USA

15. Pulley JM, Clayton E, Bernard GR, Roden DM, Masys DR. Principles of human subjects protections applied in an opt-out, de-identified biobank. Clin Transl Sci. 2010; 3(1):42–48. [PubMed: 20443953]

16▪. Harnischmacher, U.; Ihle, P.; Berger, B.; Goebel, J.; Scheller, J. Checkliste und Leitfaden zur Patienteneinwilligung: Grundlagen und Anleitung für die klinische Forschung. Medizinisch wissenschaftliche Verlagsgesellschaft; Berlin, Germany: 2006. Introduction to the German legal framework for informed consent along with suggestions for addressing issues

17▪. Reng, CM.; Debold, P.; Adelhard, K.; Pommerening, K. Generische lösungen der TMF zum datenschutz für die forschungsnetze in der medizin. Medizinisch wissenschaftliche verlagsgesellschaft; Berlin, Germany: 2006. Describes in detail the best practices for data and privacy protection for human subject research under the legal constraints in Germany

18▪. Simon, JW.; Paslack, R.; Robienski, J.; Goebel, JW.; Krawczak, M. Biomaterialbanken-Rechtliche Rahmenbedingungen. Medizinisch Wissenschaftliche Verlagsgesellschaft; Berlin, Germany: 2006. Discusses a wide range of relevant legal issues regarding the establishment and operation of a biobank in Germany and offers practical solutions

19. Langanke, M.; Erdmann, P. Die MRT als wissenschaftliche Studienuntersuchung und das Problem der Mitteilung von Zufallsbefunden, Probandenethische Herausforderungen. In: Theissen, H.; Langanke, M., editors. Tragfähige Rede von Gott, Festgabe für Heinrich Assel zum 50. Geburtstag am 9. Februar 2011. Verlag Dr. Kovac Hamburg; Germany: 2011.

20. Heinemann T, Hoppe C, Listl S, Spickhoff A, Elger CE. Zufallsbefunde bei bildgebenden Verfahren in der Hirnforschung: Ethische Überlegungen und Lösungsvorschläge. Deutsches Ärzteblatt. 2007; 104(3):1982–1987.

21. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. J Law Med Ethics. 2008; 36(2):219–248. [PubMed: 18547191]

22. Junghans C, Feder G, Hemingway H, Timmis A, Jones M. Recruiting patients to medical research: double blind randomised trial of 'opt-in' versus 'opt-out' strategies. BMJ. 2005; 331(7522):940. [PubMed: 16157604]

23. Walmsley S. Opt in or opt out: what is optimal for prenatal screening for HIV infection? CMAJ. 2003; 168(6):707–708. [PubMed: 12642426]

Websites

101. UK Biobank. Protocol for a large-scale prospective epidemiological resource. 2006. www.ukbiobank.ac.uk/docs/UKBProtocol_000.pdf

102. Bundesdatenschutzgesetz (BDSG). §3, 6a www.bfdi.bund.de/SharedDocs/Publikationen/GesetzeVerordnungen/BDSG.html?nn=408916

Executive summary

BioVU

- Biorepository at Vanderbilt University (BioVU) is a biorepository derived from de-identified electronic medical records and leftover blood samples.
- Under the US research regulations, BioVU does not qualify as human subjects research. However, extensive oversight is required to ensure that samples are not re-identified.
- In order to respect the autonomy of patients, and to ensure community approval of BioVU, patients are offered the opportunity to opt-out of having their sample included, even though US research regulations do not require this.

GANI_MED

- Greifswald Approach to Individualized Medicine (GANI_MED) is a resource that collects donated biosamples and clinical records as well as data from research-specific patient assessments.
- Participants in the GANI_MED must be re-identifiable, even though most research is conducted using de-identified data. This is because the scientific goals of GANI_MED require that patients be able to be recontacted so that longitudinal research can be performed.
- Because patients are re-identifiable, and because research-specific patient assessments are performed, GANI_MED must obtain formal patient consent. Informed consent is also indispensable for the storage of biomaterials, which are re-identifiable and not derived from routine clinical care.
- German law creates significant responsibility to secure patient data if it is potentially re-identifiable.

Future perspective

- Differing legal frameworks as well as the scientific goals of investigators inform the design of research biorepositories within the field of personalized medicine.

Table 1

Comparison between BioVU and GANI_MED.

Design consideration	BioVU	GANI_MED
Biosamples collected	Leftover blood generated through routine clinical care	Blood, urine, saliva and additional biomaterials for some diagnoses
Consent	'Opt-out'	'Opt-in'
Re-identification of data	Re-identification of the depersonalized data not allowed	Re-identification of scientific data planned to start follow-up activities at later stages
Documents	One: opt-out checkbox is included on a routine 'Consent to Treatment' form	Several: Consent form, authorization form, information booklet. Consent and authorization form are accessible in a hardcopy form as well as in a digital form
De-identification	'One way': data from inpatient and outpatient visits are added to research records without the need for re-identification. This design precludes follow-up studies and return of research results to patients	Specific re-identification possible via a trustee institution. Active follow-ups and case–control study settings possible. Research results can be returned to patients who indicate this preference on their consent forms
Data design	Both structured and unstructured data. Natural-language processing is frequently used	Data ascertainment both via research specific instruments and via export from the clinical information system. Data Dictionary facilitates analysis of data
Quality of data	No modification of routine clinical care. Quality of data depends on clinical documentation	Quality assurance during data acquisition (SOPs or standardized data collection) resulting in an intensive interaction and alteration to clinical routine care
Data access	Investigator access to data is granted through the research review process	Data requested by investigator and approved of by research committee is individually exported and transferred
Analytics	Complete separation between clinical and scientific analyses	Research data collected through routine clinical processes as well as research-specific assessments

BioVU: Biorepository at Vanderbilt University; GANI_MED: Greifswald Approach to Individualized Medicine; SOPs: Standard operation procedures