NOTES / AANTEKENINGE

INCIDENTAL FINDINGS IN BIO BANKS IN SOUTH AFRICA: ETHICAL AND LEGAL ISSUES

1 Introductory remarks

Biobanks have come to be essential apparatuses of genetic and genomic research as they are seen as essential tools for translational medicine in particular (Wolf *et al "*Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived Data Sets" 2012 14(4) *Genetics in Medicine* 361; and see also Zawati and Knoppers "International Normative Perspectives on the Return of Individual Research Results and Incidental Findings in Genomic Biobanks" 2012 14(4) *Genetics in Medicine* 484). Various unique ethical and legal challenges arise in the course of biobanking as biobanks generate a range of ethical and legal challenges related to privacy, informed consent, control and ownership, withdrawal of samples, commercialization, genomic sovereignty, return of results, incidental findings, and research governance. These issues have generated much policy debate within the international world, and yet in South Africa, debates on the ethical and legal challenges posed by biobanks and biobank networks still remain alienated.

According to Wolf, biobanks are the dominant part of a "biobank research system," consisting of primary research also known as collection sites, the biobank, and secondary research sites that access biobank data or samples for further research (Wolf *et al* "The Law of Incidental Findings in Human Subjects Research: Establishing Researchers' Duties" 2008 36(2) *Journal of Law Medicine & Ethics* 363). Therefore, incidental findings could arise at several points in a biobank-research system, that is, in primary research, biobank research, and secondary research (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 363).

Within the South African context literature and guidance are sparse on the handling of significant incidental findings which are identified in biobank systems. How incidental findings should be handled as well as the role of biobanks in enabling this process, are well-founded concerns. Unresolved in South Africa, is how to manage incidental findings of potential health, reproductive, environmental and medicinal risk that are of particular importance to individual contributors.

With a proposal for a national biobank in South Africa (Dhai "Establishing National Biobanks in South Africa: The Urgent Need for an Ethico-regulatory

Framework" 2013 6(2) *South African Journal of Bioethics and Law* 38–39 DOI:10.7196/sajbl.296 published 2013-10-24), it is apparent that researchers as well as clinicians are anticipated to access data from biobanks and to this end, laws, clear public guidance and regulations on the handling of incidental findings are indispensable.

2 What are incidental findings?

Incidental findings are results that are not associated with the aim of the research but might have significance to the participant (Slabbert "Legal Regulation of Genomics in South Africa" http://www.nstf.org.za/ShowProperty?nodePath=/NSTF%20Repository/NSTF/files/Workshops/2011/HGLegalregulation.pdf (accessed 2013-10-10)), the participant's family or the larger community.

When biobanks receive de-identified data and samples that were collected for purposes other than the biobank's research, the biobank may not be conducting human subjects' research under the Common Rule. (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 366. Common Rule stipulates that, research can be viewed as human subject research only if such research is identifiable. In other words, the identity of the research subject should be readily ascertained by the researcher. For a further discussion on the common rule, see http://bioethics.od.nih.gov/nih_third_party_rec.html (accessed 2013-12-19).) Whether the Common Rule applications affect the responsibilities of the biobank-research system which includes the responsibilities for administering incidental findings (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 366).

3 Questions raised when researchers come across "incidental findings"

The questions raised concerning incidental findings in biobanking are diverse and challenging. They include, but are not limited to, the following:

- Whether researchers within a biobank system have an ethical or legal duty to disclose incidental findings to research participants.
- If such ethical or legal duty exists, what genetic information should be disclosed to research participants? Should it be the genetic results that are considered clinically actionable?
- If disclosure of results is justified, a further question is: Who has the capacity to disclose such findings (is it the researchers, the subject's doctor, or a genetic counsellor)?
- Should research participants be aware of the likelihood of an incidental finding?
- Should research participants know about any incidental findings?
- What is the position, in circumstances where research participants do not want to accept any information on incidental findings, or want to only accept selected types of findings?

These questions raise ethical, legal, and regulatory concerns, and therefore call for consideration. This article will attempt to answer the question whether researchers have an obligation to disclose incidental findings that are clinically actionable. Limited guidance is available for addressing this question within the South African context. Seeing the proposal for the establishment of a national biobank in South Africa, and as future research on the handling of incidental findings is eminent, investigators within a biobank system must include in their protocols a reference to guidelines to their reasoning and choices regarding the handling of incidental findings. Subsequently this must be included in their consent forms. Countries such as the United States, Canada and Spain, to mention but a few, have established a pathway for handling incidental findings.

In what follows the paper discusses the ethical principles as well as the common-law principles which the authors believe will aid in channelling the regulation of incidental findings in South Africa.

The ethical principles applicable to incidental findings will mainly be drawn from the South African Medical Research Council Guidelines for Medical Research, the Medical Research Council Guidelines for Ethics in Medical Research on Reproductive Biology and Genetic Research and the South African Good Clinical Practice Guidelines. With regards to the legal principles applicable to incidental findings, the discussion considers the common-law principles applicable to the researcher and research-participant relationship in as far as they relate to the disclosure of incidental findings.

4 Grounding researchers' duties to disclose incidental findings: ethical sources

Incidental findings may be viewed as both threats and possible benefits, since they may convey vital and even life-saving clinical information, but also may be complex and far-reaching (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 366). Disclosure of incidental findings with immediate clinical significance may benefit a participant's health should they be detected early and treatment is offered. Long-term benefits of early detection of incidental findings may well include an improved quality of life, and future planning related to health status, and obviously the avoidance of the necessity for disturbing or risky treatments. Short- and long-term risks may perhaps involve anxiety associated with incidental findings, high medical expenses for participants who pursue the clinical implications of incidental findings, the burdens of follow-up, with some incidental findings turning out to be non-threatening or even false positives.

The duty to disclose incidental findings is grounded on the broader ethical concepts of

- beneficence (benefit to the research participant);
- non-maleficence (absence of harm to the research participant);
- reciprocity;
- concern for research participants' welfare;

- justice (notably distributive justice – equal distribution of risks and benefits between communities); and
- respect for participants' autonomy.

As incidental findings do inflict risks, the provisions calling for limiting of risk, and that risks ought to be reasonable in relation to foreseen benefits are appropriate (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 367). The analysis, balance and distribution of harms and benefits are critical to the ethics of human research. Contemporary research ethics, for example, entail a favourable harms-benefit balance – to be precise, that the anticipatable harms should not prevail over anticipated benefits. (South African Medical Research Council Guidelines for Medical Research 9 and 47. See also Summary of the Guiding Ethical Principles for Research Ethics, http://www.yorku.ca/igreene/tricoun.htm (accessed 2013-10-10)). The harms-benefit analysis has an impact on the welfare and rights of research participants, the informed assumption of harms and benefits, and the "ethical justification for competing research paths" (South African Medical Research Council Guidelines for Medical Research 9 and 35. See also University of Alberta, Faculty of Arts, Department of Anthropology, Guidelines for the preparation of Ethics Proposals, http://www.anthropology.ualberta.ca/en/Resources/ResearchEthics/GuidelinesforthepreparationofE.aspx (accessed 2013-10-10)).

The reciprocity principle fits within the constraints of research, personal ethics, and within the framework of maintaining one's role as investigator (South African Medical Research Council Guidelines for Medical Research 35). The ethical duty of reciprocity suggests that there should be reciprocity in what participants give and what they receive from participation in a research project (South African Medical Research Council Guidelines for Medical Research 35). Participants ought to receive feedback on research results, because this is a form of gratitude and appreciation to participants for their involvement. In recent times reciprocity has been discussed in human subject's research as an element of justice. The perspective to reciprocity refers to what people ought to receive aligned to what they have contributed in a research project (South African Medical Research Council Guidelines for Medical Research 35). Therefore, the relay of incidental findings is a noble gesture.

A further justification to disclose incidental findings is based on the respect for research participant's autonomy (South African Medical Research Council Guidelines for Medical Research 87). This principle is commonly understood as respect for persons and incorporates the ethical conviction that "individuals should be treated as autonomous agents." (South African Medical Research Council Guidelines for Medical Research 85). Such reverence proposes that research participants have a presumptive privilege to information about themselves. Respect for persons includes a respect for participants' self-determination and consequent need for information related to their health and welfare. It would be discourteous to treat research volunteers as channels for generating scientific data without giving due consideration to their interest in receiving research data about

themselves ensuing from their involvement in a research project (South African Medical Research Council Guidelines for Medical Research 85).

Research ethics literature seems to advocate that researchers may possibly owe more to participants. This ethical dialogue has been harmonized by augmented consideration in the law to participants' rights and researcher duties.

5 Duties under common law to disclose incidental findings

In order to establish negligence as a cause of action under the law of torts, a court must identify a special relationship between the parties and such relationship must create a duty of care (Medical Law Attorneys*, Malpractise and Negligence Lawsuits, Negligence,* http://legal-dictionary.thefreedictionary.com/negligence (accessed 2013-10-10)). In this regard, a plaintiff must attest to the fact that the defendant owed a duty to the plaintiff and that the defendant breached such a duty by failing to conform to the mandatory standard of conduct and that the defendant's negligent conduct was the basis of the injury to the plaintiff (Medical Law Attorneys*, Malpractise and Negligence Lawsuits, Negligence,* http://legal-dictionary.thefreedictionary.com/negligence (accessed 2013-10-10)).

The physician-patient relationship is an example of such a special relationship, and breach of consent consequently gives rise to a medical malpractice action (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Where such a doctor-patient relationship does not exist courts apply an ordinary negligence standard which is an omission to use a rational standard of care (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). In such cases researchers owe their participants the similar ordinary caution that any citizen owes his/her fellow citizens which is a standard fairly likely to be too lenient (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370).

In cases where there is an existing doctor-patient relationship, and such patients are also research subjects, courts may possibly treat such cases as a kind of medical malpractice (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370).

In South Africa, harm from a research-related injury may possibly be categorized as a delict (Singh and Strode "Compensation for Research-related Injury in South Africa: A Critique of the Good Clinical Practice (GCP) Guidelines" 2012 5(2) *South African Journal for Bioethics Law* 91). Research participants are not barred from claiming damages under civil law, although such claims necessitate the plaintiff to prove negligence (Singh and Strode 2012 5(2) *South African Journal for Bioethics Law* 91).

Two American court cases have recognized a special relationship between researchers and research participants in cases were a physician-patient relationship does not exist. *Grimes v Kennedy Krieger Institute* (*Ericka Grimes v Kennedy Krieger Institute* 366 Md. 29, 782 A.2d 807 1 cited from Westlaw educational use cases), discussed the duties of a researcher

comprehensively and this case has drawn further attention in addition to controversy.

The Grimes case involved a study on lead-paint reduction in homes leased to families with young kids (*Ericka Grimes v Kennedy Krieger Institute supra* 8–9). The investigators at Kennedy Krieger Institute (KKI) examined blood-lead levels of the kids with the intention of determining the adeptness of varying degrees of abatement (*Ericka Grimes v Kennedy Krieger Institute supra* 8–9). The research-participant plaintiffs were kids found by the research to have higher blood-lead levels; they claimed that KKI had failed to caution them of the lead-paint dangers that it knew or ought to have known to be present in the plaintiffs' homes (*Ericka Grimes v Kennedy Krieger Institute supra* 8–9). The Maryland Court of Appeals held that:

> "the very nature of nontherapeutic research on human subjects can, and normally will, create special relationships out of which duties arise" (*Ericka Grimes v Kennedy Krieger Institute supra* 31).

In the *Grimes case* the court found that researchers were in general in an enhanced position to "anticipate, discover, and understand the potential risks to the health" of research participants and established that a duty arose out of researchers' superior knowledge, since participants were "often poorly placed to protect themselves from risk" (*Ericka Grimes v Kennedy Krieger Institute supra* 48). The court found that informed consent requirements under the federal regulations created a duty of care arising out of that relationship, an infringement of which was unlawful under state law (*Ericka Grimes v Kennedy Krieger Institute supra* 54). For further backing, the court looked to the Nuremberg Code coming to the conclusion that it:

> "speaks strongly to the existence of special relationships imposing ethical duties".

Preceding the *Grimes*, the *Blaz v Michael Reese Hospital case* (*Blaz v Michael Reese Hospital case* 74 F.Supp.2d 803 (1999), *United States District Court, N.D. Illinois Eastern Division November 10, 1999,* http://www.leagle.com/decision/199987774FSupp2d803_1795 (accessed 2013-12-09), paragraph 1, Memorandum, opinion and order) established a special relationship amid researcher and research participant.

In *the Blaz case,* patients at Michael Reese Hospital Foundation were treated with x-ray therapy for benign conditions from 1930 to 1960, including the plaintiff Joel Blaz (*Blaz v Michael Reese Hospital case supra*). The Michael Reese hospital arranged a Thyroid Follow-Up Project in 1974 to collect data and do research on the patients exposed to the x-ray therapy (*Blaz v Michael Reese Hospital case supra*). The relevant people involved in the programme contacted Blaz in 1975 to inform him that he was at an increased risk of developing thyroid tumors for the reason that he had received the treatment (*Blaz v Michael Reese Hospital case supra*). The programme contacted Blaz again in 1976, offering him related information as well as appealing to him that he returned to the hospital for assessment and treatment at his private expense, but he refused (*Blaz v Michael Reese Hospital case supra*). In 1981, Dr Schneider (the physician in charge of the follow-up program) sent Blaz a letter and a questionnaire, which Blaz

received but did not return (*Blaz v Michael Reese Hospital case supra*). The contents of the letter explained in detail that the purpose of the survey was to "investigate the long-term health implications" and "to determine the possible associated risks" of the childhood-radiation treatments which Blaz and others had undertaken (*Blaz v Michael Reese Hospital case supra*). However, the contents of the letter failed to reveal the fact that the hospital had solid confirmation of a connection between the treatment and tumor development (*Blaz v Michael Reese Hospital case supra*). In 1987 Blaz was diagnosed with a neural tumor and he sued the hospital and Dr Schneider, asserting that they failed to inform him of their results which revealed that he might be at greater risk of neural tumors in a manner that ought to have allowed their earlier detection and removal or other treatment (*Blaz v Michael Reese Hospital case supra*).

The court found that:

> "[a] duty to warn exists when there is 'unequal knowledge and the defendant possessed of such knowledge, knows or should know that harm might occur if no warning is given'" (*Blaz v Michael Reese Hospital case supra*).

The court held that Dr Schneider's position of researching the consequences of treatments and contacting patients who were previously subjected to them generated a special relationship under state law that conferred a duty, even in absence of a physician-patient relationship (*Blaz v Michael Reese Hospital case supra*). The court found negligence based on the following criteria:

(1) whether the harm was "reasonably foreseeable";

(2) the likelihood of the injury;

(3) the magnitude of the burden of guarding against the injury; and

(4) the consequences of placing that burden upon the defendant.

Grimes and *Blaz* cases suggest that researchers undeniably have legitimately recognizable duties towards their research participants, even though the range of these duties is not up till now precise (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370).

Between the two cases, *Grimes* is more significant in the inquiry of incidental findings for the reason that the court established a special relationship giving rise to a duty, even if the risks of lead-paint exposure were not directly instigated by the research or the research institution (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Courts seem to be driven to enforce a legal duty when researchers may well have barred a serious harm to a research participant by revealing information (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Such concerns can likewise be stretched to other research spheres in which researchers come upon incidental findings.

According to Wolf, the discussed cases above, within a clinical context, inform that a physician may have a duty to convey information to a patient, which could obviate impending damage (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Wolf further explains that it is debatable that

these basic components are existent when dealing with incidental findings with grave clinical consequences (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Similar to the practising physician, the researcher has information of conceivable harm (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). The researcher is also in a position to deliver such information to the research participant and prevent or minimize potential damage (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370).

Accordingly, the Common Rule has been used to confirm a relationship between the researcher and the research participant prompting definite identifiable responsibilities (common rule stipulates that research can be viewed as human subject research only if such research is identifiable). The *Grimes* court also stated that the duty of informed consent generated a relationship and therefore, a duty of care within the Maryland state law (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370). Up until now, the use of the Common Rule to show a researcher's duty of care has concentrated on matters of informed consent (Wolf *et al* 2008 36(2) *Journal of Law Medicine & Ethics* 370).

Writing within a South African perspective, Rowe and Moodley argue that several metaphors have in the past been used to refer to the doctor-patient relationship (Rowe and Moodley "Patients as Consumers of Health Care in South Africa: The Ethical and Legal Implications" 2013 14(15) *BMC Medical Ethics* 4). Most of the metaphors referred to by the aforementioned authors apply appropriately to the circumstances of researchers. Relevant for this paper is the prevailing metaphor in medical ethics and law generally referred to as the "fiduciary" metaphor. A researcher in the scientific world is perceived as the bearer of a fiduciary duty to his participants. A fiduciary starring role communicates to the religious theory of stewardship and has its basis from the "law of trusts and agency" (Rowe and Moodley 2013 14(15) *BMC Medical Ethics* 4). A fiduciary is defined as a person with the authority or property to be used to the advantage of another person and the fiduciary is lawfully held to the highest standard of conduct (Rowe and Moodley 2013 14(15) *BMC Medical Ethics* 4). Being a fiduciary denotes a relationship grounded on reliance and trust (Rowe and Moodley 2013 14(15) *BMC Medical Ethics* 4). A fiduciary cannot support own benefits or those of a third party (Rowe and Moodley 2013 14(15) *BMC Medical Ethics* 4). In cases were a fiduciary has shared loyalties or a conflict of interest, there is an increased threat of the reliance and trust relationship being breached (Rowe and Moodley 2013 14(15) *BMC Medical Ethics* 4). It appears that there stand to be many comparisons between a fiduciary relationship and that of the researcher and research participant and the doctor-patient relationship. The above discussed ethical principles speak to the fact that that a researcher's most significant consideration ought to be the participants welfare.

Such researcher duties can on the one hand be seen as extending researcher duties to include a duty to warn of any risk which might be seen as compelling investigations in science or research into the boundaries of medical treatment, in other words, an extension of responsibilities of a researcher or non-practising physician. In the *Blaz cases* it was noted that

such an overlap of duties should not strike as a real worry (*Blaz v Michael Reese Hospital case supra*) since the duty was settled by a mere warning which for example in the *Blaz case* had been neither costly nor burdensome to give (*Blaz v Michael Reese Hospital case supra*). The more expensive and difficult the warning would be to provide, unquestionably, the less likely there would be a finding of responsibility (*Blaz v Michael Reese Hospital case supra*). Further, the medical researcher's legitimate aspiration for professional status as well as integrity owing to new discoveries would balance any such restraint and certainly the concern for the well-being of previous patients which every self-respecting hospital desired to have (*Blaz v Michael Reese Hospital case supra*).

In the *Blaz case* it was noted that a finding of no duty would allow physicians who manage hospital-research programmes into the danger of treatment policies aimed at exploiting the results of a particular research for their professional development and inquisitiveness without warning the patients of any risks connected with those treatments which their research discovered, however little the cost of warning. No social benefit is found in creating such a perverse incentive structure, particularly in view of the costs to the patients and society of preventable tumours and other illnesses. Preventative care is not an overriding good, but it is a considerable one.

6 Conclusion

This article has shown that research participants need to be protected from research-related harm which may emerge as a result of an omission to disclose incidental findings. Only actionable and verified incidental findings should be revealed to participants since incomplete understanding and under-researched findings of incidental findings can lead to unnecessary worry, upset and confusion. Guided by the common-law approach to incidental and the ethical principles applicable to incidental findings, this article recommends that South African authorities should put in place guidelines and legislation which directly speak to the researcher duties in relation to the handling of incidental findings. If such legislation is put in place, there is no doubt that it will strengthen the existing ethical principles and common-law principles applicable to incidental findings. Without doubt this will help research participants who have queries about compensation for research-related injury stemming from a failure to disclose actionable incidental findings. On the other hand, clear laws and guidelines will indicate a clear position regarding researcher duties in matters relating to incidental findings.

Maureen Mswela and Patricia Molusi
University of South Africa (UNISA)