

Contents

Contributors	xi
In Memoriam: Pia Erdmann.....	xv
Introduction.....	xvii

CHAPTER 1 Concept, history, and state of debate 1

Martin Langanke, Pia Erdmann[†], Wenke Liedtke, Kyle B. Brothers

1 Introduction: "Additional" findings in medical research.....	1
2 History of debate: A four-layer model.....	3
3 Lessons learned from population-based imaging	4
3.1 Quality of information	5
3.2 To tell or not to tell?.....	7
3.3 What to tell? Actionability and clinical utility.....	10
3.4 How to tell?.....	13
3.5 How to prepare participants?.....	18
3.6 How to design an appropriate research protocol	19
4 In search of an appropriate ethical framework	19
5 Conclusion.....	23
References.....	24

CHAPTER 2 Oversight, governance, and policy for making decisions about return of individual genomic findings 29

Adrian Thorogood, Ma'n Zawati, Bartha Maria Knoppers

1 Introduction.....	29
2 International legal and ethical principles.....	30
3 Planning ahead: Return of results protocols	32
4 Consent	32
5 What to return (or not).....	33
6 How to return	35
7 Children and adults who lack decisional capacity: Special considerations	36
8 Return of secondary findings versus the right of access.....	37
9 International data sharing and return	37
10 Conclusion	38
Acknowledgments	38
References.....	39

CHAPTER 3	Selecting secondary findings to report: Creating a list that suits your study	43
	Ann Katherine Major Foreman, Jonathan S. Berg	
1	Types of genomic findings	44
1.1	Multifactorial disease risks	44
1.2	Pharmacogenomics	45
1.3	Mendelian disease	46
1.4	Carrier status	47
2	Criteria for a reportable secondary finding	48
2.1	Confirmation and reporting	48
2.2	Genes	49
2.3	Actionability	49
2.4	Participant and study factors	50
2.5	Variants	52
2.6	Balancing risks and benefits	53
3	Lists	55
4	Conclusion	56
	References	57
CHAPTER 4	How secondary findings are made	59
	Kevin M. Bowling, Michelle L. Thompson, Gregory M. Cooper	
1	Secondary findings in clinical sequencing	59
2	Chapter overview	60
3	Current methods for large-scale DNA sequencing in clinical laboratories	61
4	Sequence read alignment, variant calling, and annotation	64
5	Use of variant filtration to detect or avoid secondary findings	67
6	Potential categories of secondary findings	69
7	Variant validation via alternative sequencing assay	70
8	Conclusion	71
	References	71
CHAPTER 5	Informed consent and decision-making	77
	Sebastian Schleidgen, Kyle B. Brothers	
1	Introduction	77
2	Ethical issues	78
2.1	Respect for autonomy and informed consent	78
2.2	Providing information	81
2.3	Offering options and eliciting preferences	82
2.4	Deciding what to disclose	83

43	3	Counseling challenges	85
44	3.1	Addressing barriers to understanding	85
44	3.2	Accounting for changing information	86
45	3.3	Managing therapeutic and diagnostic misconceptions	87
46	4	Approaches for addressing ethical issues and counseling challenges	89
47	4.1	Genetic counseling.....	89
48	4.2	Decision-making without formal counseling.....	89
48	5	Consent models.....	91
49	5.1	Staged consent	91
49	5.2	Modular consent	92
50	5.3	Family consent.....	93
52	5.4	Broad consent	93
53	6	Conclusion.....	94
55		References.....	95
56	CHAPTER 6	Reporting of secondary findings in genomic research: Stakeholders' attitudes and preferences	99
57		Gesine Richter, Eva De Clercq, Marcel Mertz, Alena Buyx	
59	1	Introduction and background.....	99
59	2	Why measure preferences? Normative ethical questions	101
60	2.1	Methodological answer: It depends on the validity of the empirical research.....	101
61	2.2	Epistemological answer: It depends on the intended use of the empirical data.....	102
64	2.3	Relevance of background premises for guideline development.....	106
67	2.4	Eliciting preferences for developing policies	107
69	3	How to measure preferences? Strategies and tools for eliciting preferences on secondary findings.....	109
70	3.1	Whose preferences need to be elicited?.....	109
71	3.2	Factors influencing preferences: Personal and disease related	110
71	3.3	Tools or instruments to elicit stakeholders' preferences.....	111
77	3.4	When to elicit stakeholders' preferences?	111
77	4	What has been found? Stakeholders' attitudes and perspectives.....	112
78	4.1	Professionals' attitudes toward disclosing or not disclosing: Clinicians, researchers, and IRB members.....	113
81	4.2	Participants' and lay attitudes and preferences.....	117
82			
83			

5	Summary	123
	References	125
	Further reading	132
CHAPTER 7	Disclosing genomic sequencing results	133
	Janet L. Williams	
1	Context of the research: Managing participant expectations	134
2	Characteristics of the study participants	136
2.1	Notification to participants of a sequence result	137
3	Disclosure modality and content	140
3.1	Laboratory reports of genomic findings	146
3.2	Who will return results	147
4	Summary	148
	References	149
	Further reading	152
CHAPTER 8	Implications of secondary findings for clinical contexts	155
	Michael Morrison, Harriet Teare, Gabrielle Bertier, James Buchanan, Yasmin Bylstra, Clara Gaff, Leigh Jackson, Kazuto Kato, Elke Kaufmann, Susan Kelly, Gabriel Lázaro-Muñoz, Liis Leitsalu, Lili Milani, G. Owen Schaefer, Christoph Schickhardt, Mahsa Shabani, Erin Tutty, Eva C. Winkler, Sarah Wordsworth	
1	Introduction	156
2	International approaches to genomics in clinical care and translational medicine	160
2.1	United States	160
2.2	United Kingdom	162
2.3	Australia	165
2.4	Germany	167
2.5	France	171
2.6	Canada (Quebec)	171
2.7	Singapore	173
2.8	Estonia	175
2.9	Japan	176
2.10	Summary	178
3	Emerging and future scenarios	182
3.1	Pediatric, neonatal, and prenatal genomics	183
3.2	Wellness genomics	185
3.3	Storage and return of raw sequence data in the clinical and research settings	187

.....	123
.....	125
.....	132
.....	133
ons.....	134
.....	136
.....	137
.....	140
.....	146
.....	147
.....	148
.....	149
.....	152
.....	155
.....	156
.....	160
.....	160
.....	162
.....	165
.....	167
.....	171
.....	171
.....	173
.....	175
.....	176
.....	178
.....	182
.....	183
.....	185
.....	187

4	Economic dimensions of returning secondary findings from genomics in clinical routine care.....	189
5	Discussion and conclusions	191
	References.....	194
CHAPTER 9	Secondary findings: Building a bridge to the future of ELSI.....	203
	Kyle B. Brothers, Martin Langanke, Pia Erdmann [†]	
1	Secondary findings as sentinel debate	204
2	Secondary findings as cultural crossroads	206
3	Secondary findings and the future of ELSI scholarship	207
	3.1 Reanalysis for clinical purposes	207
	3.2 Polygenic risk scores	209
	References.....	211
	Index	213