Problem Solving Through Precision Oncology

ELLEN R COPSON, PETER HALL, RUTH E BOARD, GORDON COOK, PETER SELBY

Published in association with the Association of Cancer Physicians

CLINICAL PUBLISHING

Problem Solving Through Precision Oncology

Problem Solving Through Precision Oncology

Edited by

Ellen R. Copson, BSc, MBBS, PhD, FRCP
Associate Professor of Medical Oncology, University of Southampton, Southampton; Honorary Consultant in Medical Oncology, University Hospital Southampton NHS Foundation Trust, Southampton

Peter Hall, MBChB, PhD, MRCP
Senior Lecturer in Health Economics, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; Honorary Consultant in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh; Visiting Associate Professor of Health Economics, University of Leeds, Leeds

Ruth E. Board, BSc, MBChB, PhD, FRCP
Consultant in Medical Oncology, Rosemere Cancer Foundation, Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, Preston; Honorary Senior Lecturer, University of Manchester, Manchester

Gordon Cook, MBChB, PhD, FRCP, FRCPath
Professor of Haematology and Myeloma Studies, University of Leeds, Leeds; St James's Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Peter Selby, CBE, MD, MA, DSc, FRCP, FRCR, FMedSci
Professor of Cancer Medicine, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds; Honorary President of the Association of Cancer Physicians and of the European Cancer Concord

Published in association with the Association of Cancer Physicians

CLINICAL PUBLISHING

OXFORD

CLINICAL PUBLISHING
an imprint of Atlas Medical Publishing Ltd
110 Innovation House, Parkway Court
Oxford Business Park South, Oxford OX4 2JY, UK

Tel: +44 1865 811116
Email: info@clinicalpublishing.co.uk

Web: www.clinicalpublishing.co.uk

Distributed worldwide by:
Marston Book Services Ltd
160 Eastern Avenue
Milton Park
Abingdon
Oxon OX14 4SB, UK
Tel: +44 1235 465500
Fax: +44 1235 465555
Email: trade.orders@marston.co.uk

First published 2017

A catalogue record for this book is available from the British Library.

ISBN 13 978 1 84692 111 7
ISBN e-book 978 1 84692 653 2

Series design by Pete Russell Typographic Design, Faringdon, Oxon, UK
Typeset by Ian Winter Design, Ramsden, Oxon, UK
Printed by Latimer Trend and Company Ltd, Plymouth, UK

Contents

SECTION TWO Case studies

Contributors

Dr Jean E. Abraham, Academic Honorary Consultant in Medical Oncology, Department of Oncology, University of Cambridge, Cambridge

Professor Rosamonde Banks, Professor of Biomedical Proteomics, University of Leeds, Leeds

Dr Sophie Barrett, Consultant in Medical Oncology, Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, Glasgow

Dr Colin Barrie, Specialist Registrar in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh

Dr Emma Beddowes, Academic Clinical Lecturer in Medical Oncology, Department of Oncology, University of Cambridge, Cambridge

Dr Nicolai J. Birkbak, Principal Research Associate, Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London; The Francis Crick Institute, London

Dr Ruth E. Board, Consultant in Medical Oncology, Rosemere Cancer Foundation, Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, Preston; Honorary Senior Lecturer, University of Manchester, Manchester

Dr Cathy Burton, Consultant in Haematology, St James's Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Sarah K. Byron, Senior Technical Adviser, National Institute for Health and Care Excellence, Manchester

Dr Jonathan Carmichael, Trainee in Haematology, St James's Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr M.H. Ruhe Chowdhury, Specialist Registrar in Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London

Dr Julia Cockle, Paediatric Registrar, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds

Professor Gordon Cook, Professor of Haematology and Myeloma Studies, University of Leeds, Leeds; St James's Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Ellen R. Copson, Associate Professor of Medical Oncology, University of Southampton, Southampton; Honorary Consultant in Medical Oncology, University Hospital Southampton NHS Foundation Trust, Southampton

Mr William Cross, Consultant Surgeon in Urology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Thomas Cummin, Clinical Research Fellow in Lymphoma, Southampton Clinical Trials Unit, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Andrew Davies, Consultant in Medical Oncology, University of Southampton, Southampton

Dr Lesley Dawson, Consultant in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh

Dr Leila Dorling, Medical Statistician, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge

Dr Elaine Dunwoodie, Registrar and Clinical Research Fellow in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Professor Diana M. Eccles, Honorary Consultant in Cancer Genetics, Wessex Regional Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton; Head of Cancer Sciences Academic Unit, University of Southampton, Southampton

Dr Angela Fenwick, Associate Professor of Medical Ethics and Education, Clinical Ethics and Law, University of Southampton, Southampton

Dr Charlotte Fribbens, Clinical Research Fellow, Breast Cancer Now Research Centre, Institute of Cancer Research, London; Royal Marsden NHS Foundation Trust, London

Professor Charlie Gourley, Professor of Medical Oncology, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; Honorary Consultant in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh

Dr Juliet Gray, Associate Professor and Consultant in Paediatric Oncology, University of Southampton, Southampton

Dr Geoff Hall, Senior Lecturer in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Peter Hall, Senior Lecturer in Health Economics, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; Honorary Consultant in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh; Visiting Associate Professor of Health Economics, University of Leeds, Leeds

Dr Angela Hamblin, Research Fellow in Molecular Diagnostics, Oxford Molecular Diagnostics Centre, Oxford University Hospitals NHS Trust, Oxford

Dr Mohamed Ifraz Hamid, Specialist Registrar in Haematology, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Nicola Hughes, Academic Clinical Fellow in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Mariam Jamal-Hanjani, NIHR Clinical Lecturer in Medical Oncology, Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London

Dr Adam P. Januszewski, Academic Clinical Fellow in Medical Oncology, Imperial College London, London

Mr Kapil Java, Specialty Trainee in Oral and Maxillofacial Surgery, Aintree University Hospitals NHS Foundation Trust, Liverpool

Dr Matthew W. Jenner, Consultant in Haematology, University Hospital Southampton NHS Foundation Trust, Southampton

Professor Johnathan Joffe, Consultant in Medical Oncology, Huddersfield Royal Infirmary, Calderdale and Huddersfield NHS Foundation Trust, Huddersfield

Professor Peter W.M. Johnson, Cancer Research UK Centre, University of Southampton, Southampton

Dr Christopher M. Jones, Academic Clinical Fellow in Clinical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr James Larkin, Consultant in Medical Oncology, Royal Marsden NHS Foundation Trust, London

Dr Janessa Laskin, Associate Professor, Department of Medicine, Division of Medical Oncology, University of British Columbia, Vancouver; BC Cancer Agency, Vancouver, Canada

Dr Michael Leahy, Consultant in Medical Oncology, Christie NHS Foundation Trust, Manchester

Dr Colin R. Lindsay, Research Fellow in Medical Oncology, Gustave Roussy Cancer Centre, Villejuif, France

Professor Anneke Lucassen, Consultant in Clinical Genetics, Cancer Research UK Centre, University of Southampton, Southampton; Clinical Ethics and Law, University of Southampton, Southampton

Professor Christopher McCabe, Capital Health Research Chair, University of Alberta, Edmonton, Canada

Dr Hayley S. McKenzie, Clinical Research Fellow in Medical Oncology, Cancer Research UK Centre, University of Southampton, Southampton

Dr Rasheid Mekki, Consultant in Medical Oncology, Mid Yorkshire Hospitals NHS Trust, Wakefield

Dr Michael Messenger, Deputy Director and Scientific Manager, NIHR Diagnostic Evidence Co-operative, Leeds Teaching Hospitals NHS Trust, Leeds; Head of Personalised Medicine and Health, University of Leeds, Leeds

Dr Amy Mitchell, Locum Consultant in Paediatric Oncology, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Leena Mukherjee, Specialist Registrar in Medical Oncology, University College London Hospitals NHS Foundation Trust, London

Dr Clive Mulatero, Consultant in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Salma Naheed, Specialist Trainee in Medical Oncology, Southampton Oncology Centre, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Chris Parrish, Consultant in Haematology, St James's Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Bob Phillips, Senior Clinical Academic Fellow, Centre for Reviews and Dissemination, University of York, York; Honorary Consultant in Paediatric and TYA Oncology, Leeds Children's Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Joseph J. Sacco, Clinical Senior Lecturer and Honorary Consultant in Medical Oncology, University of Liverpool, Liverpool; Clatterbridge Cancer Centre NHS Foundation Centre, Wirral

Mr Andrew G. Schache, Clinical Senior Lecturer, University of Liverpool, Liverpool; Honorary Consultant in Head and Neck Surgery, Aintree University Hospitals NHS Foundation Trust, Liverpool

Dr Anna Schuh, Consultant in Haematology, Oxford University Hospitals NHS Trust, Oxford

Professor Peter Selby, Professor of Cancer Medicine, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Jenny Seligmann, Clinical Lecturer in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Professor Matthew Seymour, Professor of Gastrointestinal Cancer Medicine, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Emily Shaw, Consultant in Histopathology, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Bethany Shinkins, Statistician/Health Economist, Test Evaluation Group, Academic Unit of Health Economics, University of Leeds, Leeds

Professor Susan Short, Professor of Clinical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Peter Simmonds, Consultant in Medical Oncology, Southampton Oncology Centre, University Hospital Southampton NHS Foundation Trust, Southampton

Dr Barbara Stanley, Specialist Registrar in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh

Dr Dan Stark, Consultant in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Catharine Sturgeon, Consultant Clinical Scientist, Edinburgh Royal Infirmary, NHS Lothian, Edinburgh

Professor Charles Swanton, Consultant in Medical Oncology, Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London; The Francis Crick Institute, London

Dr Stefan Symeonides, Senior Lecturer in Experimental Cancer Medicine, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh; Honorary Consultant in Medical Oncology, Edinburgh Cancer Centre, NHS Lothian, Edinburgh

Dr Yun Yi Tan, Specialist Registrar in Medical Oncology, Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, Glasgow

Dr Sebastian Trainor, Specialist Registrar in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Samantha Turnbull, Specialist Registrar in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Nicholas Turner, Consultant in Medical Oncology, Breast Cancer Now Research Centre, Institute of Cancer Research, Royal Marsden NHS Foundation Trust, London

Professor Timothy J. Underwood, Professor of Gastrointestinal Surgery, University of Southampton, Southampton

Dr Naveen Vasudev, Consultant in Medical Oncology, Leeds Cancer Centre, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds

Mr Malcolm A. West, NIHR Clinical Academic in Surgery, Academic Unit of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton

Dr Simone Wilkins, Consultant in Paediatric and TYA Oncology, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Alexandre Zougman, Team Leader in Clinical Proteomics, University of Leeds, Leeds

Preface

We have seen remarkable progress in the management of cancer. More than half of cancer patients can now expect to achieve long-term survival and cure in the UK, and slightly more in countries with the very best cancer outcomes. This progress, however, has been achieved at the cost of toxicity for cancer patients and financial cost to their healthcare economies. Oncology has historically been an imprecise medical discipline that has relied heavily on empirical evidence. We generally have not been able to predict with accuracy which patients will benefit and which have the best chance of cure. Treatments are associated with toxicity as well as efficacy because we cannot precisely target the cancer. Our choice of treatment has been determined by historical probabilities and clinical characteristics because we generally lacked the means to test a cancer to determine which treatments will work and which will not. This background makes the advent of precision medicine as precision oncology especially exciting for cancer patients and cancer professionals. The dramatic advances that we have seen in our knowledge of the fundamental biology of cancer, genomics, the transcriptome and other aspects of the phenotype are now genuinely informing the tests that tell us how a cancer is likely to behave, and the treatments that we can use to influence that behaviour.

Discussions of precision oncology are often couched in highly scientific terms, bringing molecular biology, molecular genetics, proteomics and sophisticated imaging to bear on the diagnosis, prognosis and selection of treatment for a cancer. The challenges to delivering precision oncology, however, lie not only at the cutting edge of modern science but also in the way we provide cancer care and how we organize ourselves to do so. We need to communicate effectively with patients in order to personalize their care and provide them with clear choices. Organization and logistics are important themes in precision oncology. We have a growing portfolio of molecular tests to determine the behaviour of a cancer and to predict its response to therapy. We need to look carefully, however, at how they can be deployed in a hard-pressed healthcare system to bring benefits to the maximum number of patients, in the quickest time, and in the most cost-effective way. We need to be careful that the intuitive appeal of molecular testing to guide therapy does not lead us to exaggerate the potential benefits, and keep a clear-eyed view of the evidence.

This most recent book in the Association of Cancer Physicians' prize-winning *Problem Solving* series seeks to bring out in an accessible way the potential of precision oncology and its challenges and pitfalls. Fifteen chapters are written by leading authorities in the field to give an overview of the development of precision oncology at a molecular, clinical and patient-centred level. The 21 individual case histories are then used to illustrate how precision oncology can and should be woven into the practice of cancer medicine and the organization of healthcare services. The approach is broad and inclusive and covers all currently topical aspects of precision oncology. This is a fast-moving field and the principles that are described will be enduring, although the individual tests and the individual treatments are likely to evolve rapidly in the coming decade.

Precision oncology offers to patients the prospect of more effective treatments and the avoidance of unnecessary toxicity from treatments that do not work. Patients and patient advocates see this as a vitally important goal for oncology. The potential for improving the well-being and outcomes of treatment for cancer patients through precision oncology, and the challenge of delivering it effectively and quickly, are immense.

Ellen R. Copson, Peter Hall, Ruth E. Board, Gordon Cook and Peter Selby, Editors
Johnathan Joffe, Chairman, Association of Cancer Physicians
Peter W.M. Johnson, Chief Clinician, Cancer Research UK

Acknowledgements

Editors' acknowledgements

The editors and authors are grateful to all the patients who have inspired them to prepare this book and to work together to improve patient care.

The editors warmly acknowledge the support they have received in preparing this book. They are especially grateful to Cancer Research UK for their sponsorship of the book and the workshop that preceded it, without which the whole project would not have been possible.

The editors, authors and publisher are most grateful to the Executive Committee of the Association of Cancer Physicians for their support and advice during the development of this book.

The editors thank Beverley Martin and colleagues at Clinical Publishing for their expert work in preparing the book, and Nicole Goldman, who coordinated and oversaw the book's preparation and organization.

Dr Copson would like to acknowledge the support of the University of Southampton and University Hospital Southampton NHS Foundation Trust. Dr Hall would like to acknowledge the support of the University of Edinburgh and Western General Hospital, NHS Lothian. Dr Board would like to acknowledge the support of the University of Manchester and Lancashire Teaching Hospitals NHS Foundation Trust. Professor Cook and Professor Selby would like to acknowledge the support of the University of Leeds, Leeds Teaching Hospitals NHS Trust, the National Institute for Health Research (NIHR) and the European Research Council. The book was prepared in association with the NIHR Diagnostic Evidence Co-operative Leeds, of which Gordon Cook and Peter Selby are directors and for which Peter Hall leads in health economics.

Ellen R. Copson, Peter Hall, Ruth E. Board, Gordon Cook and Peter Selby

Association of Cancer Physicians

The *Problem Solving* series of cancer-related books is developed and prepared by the Association of Cancer Physicians, often in partnership with one or more other specialist medical organizations. As the representative body for medical oncologists in the UK, the Association of Cancer Physicians has a broad set of aims, one of which is education of its own members and of non-members, including interested clinicians, healthcare professionals and the public. The *Problem Solving* series is a planned sequence of publications that derive from a programme of annual scientific workshops initiated in 2014 with 'Problem Solving in Acute Oncology', followed by 'Problem Solving in Older Cancer Patients', 'Problem Solving Through Precision Oncology' and, most recently, 'Problem Solving in Patient-Centred and Integrated Cancer Care'.

The publications involve considerable work from members and other contributors; this work has been done without remuneration, as an educational service. The books have been well received and we are delighted with their standard. *Problem Solving in Older Cancer Patients* was awarded the 2016 BMA prize for best oncology book of the year.

The Association of Cancer Physicians wishes to thank all the contributors to this and previous books, and to those yet to come.

Johnathan Joffe, Chairman, Association of Cancer Physicians

Abbreviations

ABC	Activated B cell
ABL	Abelson murine leukaemia viral oncogene homologue 1
AFP	Alpha-fetoprotein
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie [German Gynaecological Oncology Working Group]
Akt	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukaemia
ASCT	Autologous stem cell transplant
ATP	Adenosine triphosphate
BCL	B cell lymphoma protein
BCR	Breakpoint cluster region
BEP	Bleomycin, etoposide, cisplatin
BiTE	Bi-specific T cell engager
BRAF	Serine/threonine-protein kinase B-Raf
BSO	Bilateral salpingo-oophorectomy
BTK	Bruton's tyrosine kinase
CA9	Carbonic anhydrase 9
CD	Cluster of differentiation
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CK-7	Cytokeratin 7
CMI	Caris Molecular Intelligence
CODOX-M	Cyclophosphamide, vincristine, doxorubicin, methotrexate
CPET	Cardiopulmonary exercise test
CRAF	RAF proto-oncogene serine/threonine-protein kinase C-Raf
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CSG	Cancer susceptibility gene
ctDNA	Circulating tumour DNA
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
CXCL12	C-X-C motif chemokine 12
CYP	Cytochrome P450
DCIS	Ductal carcinoma *in situ*
DEC	Diagnostic Evidence Co-operative
DLBCL	Diffuse large B cell lymphoma
DOG-1	Discovered on GIST-1
DRE	Digital rectal examination
ECX	Epirubicin, cisplatin, capecitabine
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
ELF	Enhanced Liver Fibrosis
EPOCH-R	Rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin
ER	Oestrogen receptor
ERK	Extracellular signal-regulated kinase
EZH2	Enhancer of zeste homologue 2
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence *in situ* hybridization
FOLFIRI	Fluorouracil, folinic acid, irinotecan
FOLFOX	Fluorouracil, folinic acid, oxaliplatin
5-FU	Fluorouracil
GCB	Germinal centre B cell
GERCOR	Groupe Coopérateur Multidisciplinaire en Oncologie
GIST	Gastrointestinal stromal tumour
GOJ	Gastro-oesophageal junction
GWAS	Genome-wide association study
hCG	Human chorionic gonadotrophin
HER2	Human epidermal growth factor receptor 2

HGBL	High-grade B cell lymphoma
HGSOC	High-grade serous ovarian carcinoma
HIF	Hypoxia-inducible factor
HNPCC	Hereditary non-polyposis colorectal cancer
HPF	High-powered field
HPV	Human papillomavirus
IAP	Immunosuppressive acidic protein
IGF-1R	Insulin-like growth factor 1 receptor
IGFBP	Insulin-like growth factor binding protein
IgG	Immunoglobulin G
IPI	International Prognostic Index
IRS	Intergroup Rhabdomyosarcoma Study Group
ISH	*In situ* hybridization
ISS	International Staging System
IVA	Ifosfamide, vincristine, dactinomycin
IVAC	Ifosfamide, etoposide, cytarabine
IVD	*In vitro* diagnostics
JAK2	Janus kinase 2
KIM-1	Kidney injury molecule-1
KRAS	KRAS proto-oncogene
LDH	Lactate dehydrogenase
LFS	Li–Fraumeni syndrome
LS	Lynch syndrome
MAPK	Mitogen-activated protein kinase
MDT	Multidisciplinary team
MEK	Mitogen-activated protein kinase kinase
miRNA	MicroRNA
MLH	MutL protein homologue
MMP	Matrix metalloproteinase
MMR	Mismatch repair
mRCC	Metastatic renal cell carcinoma
MRD	Minimal residual disease
MSH	MutS protein homologue
MSI	Microsatellite instability
mTOR	Mechanistic target of rapamycin
NAC	Neoadjuvant chemotherapy
NACRT	Neoadjuvant chemoradiotherapy
NCI	National Cancer Institute
NFκB	Nuclear factor kappa B
NGS	Next generation sequencing
NIHR	National Institute for Health Research
NLR	Nucleotide-binding domain and leucine-rich repeat containing receptor
NMP	Nuclear matrix protein
NOS	Not otherwise specified
NRAS	NRAS proto-oncogene
NSCLC	Non-small-cell lung carcinoma
NSTGCT	Non-seminomatous testicular germ cell tumour
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OPSCC	Oropharyngeal squamous cell carcinoma
OS	Overall survival
p53	Tumour protein p53
PARP	Poly (adenosine diphosphate-ribose) polymerase
pCR	Pathological complete response
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PI3KCA	Phosphatidylinositol 3-kinase catalytic subunit alpha
PKC	Protein kinase C
PMBL	Primary mediastinal B cell lymphoma
PMS2	Postmeiotic segregation 1 homologue 2
POG	Personalized Oncogenomics

PR	Progesterone receptor
PS	Performance status
PSA	Prostate-specific antigen
PTEN	Phosphatase and tensin homologue
QALY	Quality-adjusted life year
QOL	Quality of life
QTc	Corrected QT interval
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma
RCC	Renal cell carcinoma
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CODOX-M	Cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine, rituximab
RCT	Randomized controlled trial
RFS	Recurrence-free survival
R-IPI	Revised International Prognostic Index
R-IVAC	Rituximab, ifosfamide, etoposide, cytarabine
RTK	Receptor tyrosine kinase
SAA	Serum amyloid A
SCC	Squamous cell carcinoma
SHH	Sonic hedgehog
SLAMF7	Signalling lymphocytic activation molecule F7
SNP	Single nucleotide polymorphism
STAT3	Signal transducer and activator of transcription 3
SYK	Spleen tyrosine kinase
TB	Tuberculosis
TdT	Terminal deoxynucleotidyl transferase
TGCT	Testicular germ cell tumour
TGF	Transforming growth factor
TKI	Tyrosine kinase inhibitor
TNF	Tumour necrosis factor
TNT	Triple-negative tumour
TTF-1	Thyroid transcription factor 1
VAF	Variant allele frequency
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel–Lindau
VUS	Variant of unknown significance
Wnt	Wingless/Int-1

PERSPECTIVE

15 Ethical Issues in Precision Oncology/Cancer Genetics

Angela Fenwick, Anneke Lucassen

Introduction

Precision medicine promises treatments that are tailor-made to the individual. An individual's genetic make-up, or the particular genetic changes in the cancer they have, may allow targeting of treatments to individual genomic variations. Such precision tailoring has been made more affordable and feasible by the advent of new, rapid genomic technologies such as whole genome sequencing. These new technologies bring a sea change in medicine, but they also bring ethical challenges. Whilst none of these is unique to genomics, there are some that merit special attention as the technical advances continue at an astounding pace.

In this chapter we outline some key issues and some of the questions raised by new genomic technologies. In particular, we focus on some of the familial tensions that may arise from germline genomic information; genomic information from analysis of the tumour itself does not generally raise these issues.

Confidentiality

Germline genomic information is to some extent both familial (i.e. it is information shared by, and therefore of potential relevance to, other family members) and personal to an individual. Much like in the medical management of infectious diseases, there may be times when healthcare professionals want to alert relatives to the risk they have discovered in an individual. This may never be a problem if individuals are willing to share relevant information with family members, and do so effectively. An example might be the discovery of a *BRCA1*/*BRCA2* mutation in one person, which confers a high risk of cancer: issues can arise if a patient is not willing, or able, to share the information with relatives, or where a healthcare professional has information but is unsure whether relatives are aware of their risk.

Although UK General Medical Council guidance gives genomic information as one example where confidentiality is not absolute and where it may be appropriate to share information without consent with at-risk relatives, there are still many situations in which professionals may be very unsure as to what their responsibilities to family members are; for example, with whom should the onus lie for such communication? When should healthcare professionals feel obliged to inform others, or even to breach their patient's confidentiality? Given that different inherited mutations may result in different lifetime risks of cancer, what level of risk would sway the balance? Do healthcare professionals have more of a responsibility to ensure the information is communicated when there are surveillance or treatment options that could potentially prevent harm to at-risk relatives? Furthermore, do family members have a right to know that they are at risk even if no interventions are available? If they do, who has an obligation to ensure this right is realized?

Traditional approaches to patient care, which view confidentiality as a principle applicable to individuals, can raise difficulties for healthcare professionals when they know the information

(potentially) applies to more than one person. Arguably, this situation may be reinforced if genomic medicine is described as 'personalized' medicine. One way around this tension might be to distinguish genomic and clinical information, even though the two may be closely related; for example, clinical information about an ovarian cancer is individual, whilst the inherited gene mutation that predisposes is familial. If genomic confidentiality is viewed at a familial, rather than an individual, level it is possible to start with the premise that information should be shared with at-risk relatives unless there are compelling reasons not to do so. This is the reverse of the individualized approach, where the default position is that information should be held in confidence unless serious harm can be prevented by breaching such confidence. Information may be able to be shared ('there is an inherited tendency of breast cancer in your family') without revealing personal information ('Jane has breast cancer'), even if, as a consequence, inferences between the two could be made.

Incidental findings

The possibility of genetic tests revealing incidental findings (not related to the original reason for the test) is not new, but, with the advent of whole genome sequencing, its likelihood is increased and, indeed, depending on the level of interrogation of a genome sequence, incidental findings may come to be seen as expected rather than unexpected. Incidental findings range from risk factors with varying degrees of evidence, or available intervention, to certain predictions or diagnoses. Some may only be confirmed after additional testing, following which they may still have uncertain clinical significance. They can complicate consent and disclosure practices; for example, to what extent can patients give valid consent to a test if they do not have detailed information about what the test might reveal, and when should findings then be disclosed?

The debate about incidental findings has often assumed that the finding itself is clear and highly predictive, but currently much genomic information is often far from this, raising questions about how high the risk, or how certain the risk, needs to be before such information should be communicated to patients. The 'fully informed consent' mantra of recent years is not realistic in genomics, so what type of consent is possible and acceptable? Some have suggested consent to broad categories of findings, such as those with 'clinical utility', but this type of approach also has problems, as patients and professionals may disagree as to what this constitutes. Furthermore, if a decision is made not to disclose information that has no currently known clinical utility, should healthcare professionals have an obligation to follow up patients and disclose at some future point if the information is found to have utility?

Testing children

Genetic testing of children might be undertaken to diagnose and treat inherited cancers that manifest in childhood, but whole genome sequencing may also predict risks of cancer with an onset in adulthood. Determining adult-onset risks in children, before they are able to decide for themselves whether and when they wish to know about their inheritance (about which nothing can be done until adulthood), raises its own ethical concerns. There is well-established professional consensus that unless testing has current medical benefit, or is in the child's best interest, it should be deferred until a child is old enough to make his or her own decision about whether and when testing should be done.

Predictive information about adult-onset cancer predispositions is more likely to be revealed from whole genome sequencing than from targeted genetic testing. For example, in a child who has whole genome sequencing for current unrelated problems, it might reveal an adult risk of

breast cancer. Should the result be disclosed to parents or kept somewhere for the child to access in the future? Who has responsibility to follow up the future adult, if and when the information has clinical utility? Given recommendations to delay testing for adult-onset conditions, should such risks always be excluded from the analysis in the first place? But what if this type of result could prevent harm to an adult family member from whom the child has inherited the condition? Some have argued that the potential disadvantage to the child is offset by the advantage to the parent who may not yet be aware of his or her own risk.

Prenatal and preconception screening

Genomic testing is also possible before birth: during pregnancy, before implantation or even before conception. In families with strongly inherited cancer predispositions, pre-implantation genetic diagnosis is sometimes requested so that difficult decisions about termination of an affected pregnancy can be avoided. The costs and success rates, and the fact that some inherited predispositions have a less than full penetrance, mean, however, that these remain difficult decisions for individuals or couples.

Prenatal genomic tests may provide diagnostic information about abnormalities (e.g. high-risk cancer genes detected in a pregnancy). The broader the testing the greater the possibility of finding variants in a fetus where the health risk is uncertain, raising similar questions, as with incidental findings, about valid consent. Women who undergo broad prenatal testing will receive information about the fetus which they may want to use to make decisions about terminating a pregnancy. They may be faced with information that gives the fetus an increased risk of cancer, but it may be hard to know what to do with this information, especially if the earliest onset is not until adulthood. Alternatively, the information may be difficult to interpret or is easily misunderstood (e.g. being seen as having more predictive power, and so more anxiety provoking, than is the case), leading to unnecessary terminations of pregnancy. Other ethical issues include: what should happen to the information and to whom should it be disclosed, and when? How should it be stored for future use, and can current health systems cope with such long-term storage and recall?

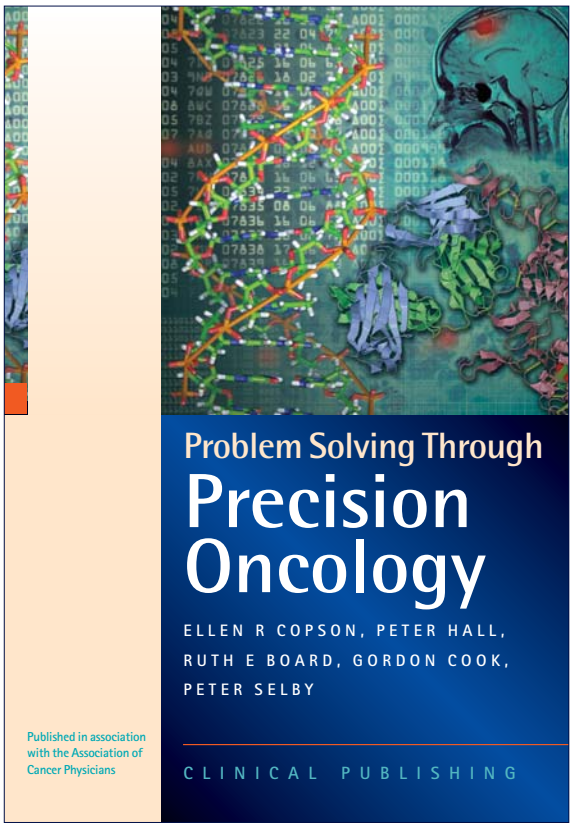
More generally, systems will need to be set in place for referral to the appropriate specialists, at the right time, especially if the genomic test is instigated by a professional who has little expertise in the particular genomic finding (such as a community paediatrician discovering an adult-onset bowel cancer predisposition).

Conclusion

Precision medicine using genomic technologies hails advances in diagnosis and treatment in a range of cancers. At the same time, the technological advances leave in their wake ethical issues that require further careful consideration if the promises of these advances are to be realized.

Further reading

- Bredenoord AL, Onland-Moret NC, Van Delden JJ. Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy. *Hum Mutat* 2011; 32: 861–7.
- Crawford C, Foulds N, Fenwick A, *et al.* Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. *Genet Med* 2013; 15: 896–9.
- Dheensa S, Fenwick A, Lucassen A. 'Is this knowledge mine and nobody else's? I don't feel that.' Patient views about consent, confidentiality and information-sharing in genetic medicine. *J Med Ethics* 2016; 42: 174–9.
- Dheensa S, Fenwick A, Shkedi-Rafid S, *et al.* Health-care professionals' responsibility to patients' relatives in genetic medicine: a systematic review and synthesis of empirical research. *Genet Med* 2016; 18: 1–12.
- Lucassen A, Parker MP. Confidentiality and sharing genetic information with relatives. *Lancet* 2010; 275: 1507–9.
- Shkedi-Rafid S, Dheensa S, Crawford G, *et al.* Defining and managing incidental findings in genetic and genomic practice. *J Med Genet* 2014; 11: 715–23.



Ellen R. Copson, Peter Hall, Ruth E. Board, Gordon Cook, Peter Selby, editors.

Problem Solving Through Precision Oncology

Oxford: Clinical Publishing; 2017.

ISBN 978 1 84692 111 7

Problem Solving Though Precision Oncology

From the Preface: 'The potential for improving the wellbeing and the outcomes of treatment for cancer patients through precision oncology, and the challenge of delivering it effectively and quickly, are both immense.'

Precision oncology enables better prevention strategies and ensures that therapeutic interventions can be concentrated on those who will benefit, reducing expense and sparing side effects for those who will not. This new educational resource provides a practical review of the latest progress in this cutting-edge area of clinical practice.

Fifteen chapters written by leading authorities in the field give an overview of the development of precision oncology at a molecular, clinical and patient-centred level. Individual case histories then illustrate how precision oncology can be and should be woven into the practice of cancer medicine and the organisation of healthcare services.

This book provides an understanding of the underlying principles of precision oncology, and a map of future developments. It is an invaluable companion for oncologists in practice and training, surgeons, general physicians, oncology nurses, GPs, clinical scientists, strategic and operations managers in healthcare services.

Related titles:

Problem Solving in Older Cancer Patients
A RING, D HARARI, T KALSI, J MANSI, P SELBY
ISBN 978 1 84692 110 0

Problem Solving in Acute Oncology
E MARSHALL, A YOUNG, P CLARK, P SELBY
ISBN 978 1 84692 108 7

Problem Solving in Oncology
D O'DONNELL, M LEAHY, M MARPLES, A PROTHEROE, P SELBY
ISBN 978 1 904392 84 2

CLINICAL PUBLISHING
www.clinicalpublishing.co.uk

ISBN 978-1-84692-111-7
9 781846 921117 >