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

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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
Contributors

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
Editors’ acknowledgements

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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

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

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

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

Background
The principle of personalized medicine, which aims to deliver a management schedule based on the attributes of the individual rather than on the whole population with the same diagnosis, has always been particularly attractive in oncology. Identification of patients who will receive maximum benefit from aggressive treatment regimens as well as those who will not benefit from standard therapies has the potential to improve cure rates in early disease, reduce the risk of toxicity and improve quality of life in advanced cancer. Historically, however, cancer has largely been treated simply on the basis of the anatomical site and extent of the disease using cytotoxic drugs that cause significant collateral damage through a tendency to identify malignant cells only by their rapid movement through the cell cycle. Prior to 1990, drugs that recognized cancer cells in a more targeted fashion did exist, but their use was largely unselected; for example, the anti-oestrogen tamoxifen was originally given to all breast cancer patients. Its use was only limited to oestrogen receptor-positive patients after retrospective data published some 30 years later showed clear evidence of effectiveness only in this subgroup.

Use of biomarkers to measure disease course or treatment responsiveness has also largely relied on circulating protein ‘tumour markers’, which vary significantly from one patient to another in terms of their specificity and clinical utility. Important exceptions are alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG), which have gained clinical acceptability as useful prognostic markers of germ cell cancer. The production of trastuzumab, a humanized monoclonal antibody specifically designed to bind to a protein overexpressed on the cell surface in an aggressive subgroup of breast cancers was a pivotal development in oncology. The success of this drug, which combines clinical effectiveness with a preferable toxicity profile to conventional cytotoxics, has been followed by the development of many other antibodies and small molecules designed to match newly identified tumour features.

Recent developments
The completion of the Human Genome Project in 2000 heralded a new era in cancer biology. We now know that there are typically between 1000 and 10,000 somatic genetic changes in the genomes of most adult cancers. The mutational landscapes of many tumours have been made publicly available through projects such as The Cancer Genome Atlas project. Identification of the key driver mutations in some tumour types has permitted the development of a number of therapeutic agents that specifically target the aberrant protein product. In current clinical practice the abnormal protein or genetic fault is usually detected using tests developed to detect that specific tumour-associated change. More recently, however, with massive advances in genomic technologies over the last decade, it is now feasible and potentially cost-effective to directly examine the whole DNA sequence of an individual tumour specimen in a timely fashion in order both to predict response to novel targeted therapies and to increase our prognostic accuracy by categorizing disease subtypes at a molecular level. The feasibility of large-scale
tumour genomic testing in the NHS has been demonstrated by the success of the first phase of the Cancer Research UK Stratified Medicine Programme in which >40,000 genetic tests were performed on over 9000 patient tumour samples at three central laboratories during a 2 year pilot study.

Provision of tumour genomic profiling in a timely fashion has resulted in a wave of new clinical trial designs, in which patients, often from a broad spectrum of solid tumour types, are admitted to a trial on the basis of broad clinical eligibility criteria, and subsequent treatment allocations or randomizations are contingent on the presence or absence of specific somatic mutations. Such trials are increasingly offering a ‘basket’ of targeted agents as treatment arms, frequently supplied by more than one pharmaceutical company.

In addition, use of the same technology on germline DNA samples has permitted the advent of fast track testing for inherited mutations in cancer predisposition genes. This, together with advances in our understanding of the biology of certain cancer susceptibility syndromes and the development of drugs which specifically aim to exploit the inherited genetic variation, is increasingly bringing genetic testing out of specialist clinics and into mainstream oncology. Identification of rare DNA variants associated with enhanced toxicity to specific chemotherapeutic agents has also become possible and is starting to enter routine clinical practice.

In parallel with the advances in genomics, other tools to analyse changes in cell biology and the proteomics of cancers and patients are becoming more powerful, faster and cheaper. They are slowly but clearly adding to our ability to identify new markers to support precision oncology and to evaluate them thoroughly. Clinical research to evaluate the effectiveness of precision oncology strategies will increasingly benefit from developments in methodologies in informatics and applied health research.

**The rewards**

The introduction of novel anticancer drugs designed to target aberrant proteins specific to the malignant tumour has already resulted in some impressive advances in certain solid tumours. Metastatic melanoma has traditionally been associated with extremely poor survival due to a relative lack of chemosensitivity. Identification of the driver gene mutation \(BRAF\) V600E in approximately half of patients with metastatic melanoma led to trials of serine/threonine-protein kinase B-Raf (BRAF) kinase inhibitors in this patient group. A phase III trial comparing use of the BRAF inhibitor vemurafenib in melanoma patients with standard chemotherapy dacarbazine reported a significant increase in progression-free survival (PFS) among those who received vemurafenib. Similar results have subsequently been reported with the alternative BRAF inhibitor dabrafenib.

Advances in our understanding of the mutational landscape of non-small-cell lung carcinoma (NSCLC) have already resulted in changes in the standard management of this group of patients. Several tyrosine kinase inhibitors are now approved for use in the 10–40% of NSCLC patients whose tumours harbour mutations in \(EGFR\), the epidermal growth factor receptor gene, following clinical trials reporting response rates of up to 80% and higher median survival than with conventional chemotherapies. Rearrangements of the \(ALK\) gene are also now being tested routinely in selected NSCLC patients following licensing of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib as a second line therapy for this patient group.

A recent multivariable analysis of clinical trial data from 641 studies reported that personalized therapy compared with non-personalized therapy was associated with a higher response rate
(31% vs 10.5%), prolonged PFS (5.9 vs 2.7 months) and longer overall survival (13.7 vs 8.9 months), whilst another meta-analysis including over 38,000 patients also demonstrated improved outcomes with personalized treatment approaches.\footnote{7}

Use of genomic tumour profiling to predict benefit from traditional chemotherapy has also now been successfully introduced into the clinic. In 2013, NICE approved the funding of Oncotype DX (Genomic Health, London, UK), a commercial genomic assay that compares expression of 16 genes implicated in breast cancer prognosis with five reference genes to produce a ‘recurrence score’. This provides selected breast cancer patients with enhanced information about their individual benefit from adjuvant chemotherapy. A number of similar tests are also now under evaluation in clinical trials.

**The challenges**

Despite the encouraging results of meta-analyses reviewing the benefit of personalized anticancer therapies, the only prospective trial to date randomizing patients with advanced cancer to either a targeted treatment based on molecular tumour profiling or treatment of physician’s choice has recently reported disappointing results. The Randomized Phase II Trial Comparing Therapy Based on Tumor Molecular Profiling versus Conventional Therapy in Patients with Refractory Cancer (SHIV A) trial\footnote{8} found no significant difference in PFS between the two treatment arms and more toxicity with the targeted therapies. The full trial report demonstrates many of the difficulties now being recognized as challenges to fulfilment of the potential of precision oncology.

The first practical issue is the need to provide high-quality DNA in sufficient quantities for successful sequencing; thus, the ideal source of tumour DNA is a fresh-frozen tumour sample of sufficient size.\footnote{4} This may therefore require patients to have additional biopsies beyond those normally required for diagnostic purposes. Secondly, our rapidly developing appreciation of the heterogeneity of solid tumours suggests that a single site biopsy at a single time point will provide only limited information. Traditionally genomic testing is done on the primary tumour biopsy, which may not reflect the true DNA sequence of a metastatic deposit. Thirdly, the vast amount of data produced particularly by whole genome sequencing and uncertainties over the reporting of variants as well as difficulties in identifying driver and passenger mutations mean that producing a genomic profile report in a timescale where it can be of benefit to a patient is a significant challenge. Fourthly, introduction of routine genomic testing and targeted therapies will require significant financial investment. Finally, there are unique ethical questions raised by this new availability of heritable genetic data.

**The future**

Most clinical trials to date have used parallel tests of a panel of frequently mutated genes relevant to cancer to demonstrate significant germline or somatic DNA variations. The rapid reduction in sequencing costs has led to increasing use of whole genome sequencing as both an exploratory research tool and as a clinical test. There is also increasing interest in the concept of liquid biopsies,\footnote{9} which use repeated peripheral blood tests to capture tumour genomic data via circulating tumour DNA in order to provide a longitudinal picture of metastatic cancer as it evolves. The use of high-throughput large data technologies (‘omics’) is already extending beyond DNA and into the analysis of RNA, protein and metabolites with the aim of identifying highly sensitive and specific novel biomarkers that will permit identification and monitoring of cancers in a previously unknown manner. This is all leading to a paradigm shift in the perception
Figure 1.1: Personalized medicine strategy as presented by Sir Bruce Keogh in a Board Paper to NHS England, 24 September 2015.

- Low-cost 'at-risk' tests
- Low-cost prevention therapy
- Automated disease registry
- Predict future disease
- Personalized treatment plan
- Predisposition to drug response
- Makes subpopulation therapy more economic
- Conditions identified and managed at an early stage
- Fewer patients getting cancer and other diseases
- Greater efficiency from streamlined care pathways
- Improved patient experience through more participation
- Therapies only used when indicated
- Fewer unwanted side effects/adverse events
- Conditions identified and managed at an early stage
- Evidence-based course of action
- Personalized medicine strategy
- Precise diagnosis based on underlying cause, rather than just grouped symptoms
- Early identification of disease
- Identification of predisposition markers or underlying processes can predict future disease
- Precise diagnosis
- Effective treatments
- Improved outcomes
- Improved patient experience through more participation
- Fewer unwanted side effects/adverse events
- Conditions identified and managed at an early stage
- Evidence-based course of action
- Personalized medicine strategy
- Precise diagnosis based on underlying cause, rather than just grouped symptoms
- Early identification of disease
- Identification of predisposition markers or underlying processes can predict future disease
- Precise diagnosis
- Effective treatments
- Improved outcomes
of personalized cancer care with the potential use of germline and somatic genomic, transcriptomic, proteinomic and metabolomic profiles to facilitate diagnosis and treatment selection for cancer patients as well as to inform cancer prevention and screening strategies for at-risk individuals, thus providing a precision oncology approach.

The role of precision medicine as a means to improve the cost-effectiveness of modern healthcare has recently been highlighted in an NHS White Paper, presented by Sir Bruce Keogh (Figure 1.1). Support from the Department of Health for the concept of precision medicine has resulted in government funding of the 100,000 Genomes Project, a highly ambitious project which is aiming to perform whole genome sequencing on 50,000 genomes from cancer patients (germline and tumour) in addition to genomes from families with rare diseases, and pathogens. This project is jointly managed by NHS England and Genomics England and has been envisaged as a transformative project that will embed genomic medicine into routine NHS patient care whilst also promoting the UK as a world leader in genomic technologies and research. NHS patients are currently being recruited into the cancer arm via regional genomic medicine centres in England, but it is anticipated that Scotland and Wales will be involved as the project progresses. A novel aspect of this project is that genomic medicine centres are obliged to inform participating patients about any 'actionable' genomic results, and patients can also opt to receive information about additional genetic findings that are not related to their primary cancer but that might benefit their long-term health. At present, few patients will receive somatic tumour information in a timeframe that would affect management of their primary cancer, but the project is aiming to achieve this within its lifetime.

The successful implementation of precision oncology will require attention to the following issues:

- Robust data collection linking clinical and pathological phenotypes to tumour and germline genotypes and treatment response data.
- Establishment of agreed standards in molecular pathology including processing methods, reporting formats, turnaround times and integration of molecular and histopathological results.
- Training of relevant multidisciplinary teams and individual professionals in genomics, in order to understand report results and their implications for management, as well as the relative merits and limitations of different techniques used for genomic analysis.
- The need to ensure that molecular testing and consequent clinical recommendations are rigorously assessed with high-quality study designs and are appropriately funded at national levels.

Conclusion

Precision oncology offers a hugely exciting opportunity to personalize cancer treatments for the benefit of the individual, but it also presents great challenges, both scientific and ethical. It will remain essential to pursue evidence-based medicine; whether it is appropriate to prescribe off-licence on the basis of genomic profiling without clear evidence of benefit outside a clinical trial remains a matter of debate. Delivery of this new era of cancer care will require a new type of multidisciplinary model involving oncologists, geneticists, cellular and molecular pathologists, information technology experts and bioinformaticians.
References


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

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