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A Bioinformatics Approach to
Synthetic Lethal Interactions in
Breast Cancer with Gene
Expression Data

S. Thomas Kelly

a thesis submitted for the degree of
Doctor of Philosophy
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New Zealand.

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Abstract

Background

Synthetic lethal genetic interactions are re-emerging in the post-genomics era due to their potential for use in precision medicine against cancers. Synthetic lethal drug design exploits the functional redundancy of genes disrupted in cancers (including tumour suppressors) to develop specific treatments against them. *CDH1*, which encodes [E-cadherin](#), is a tumour suppressor gene with loss of function in breast and stomach cancers. Experimental screens have identified candidate synthetic lethal interactions for drug target triage, which can be further supported with bioinformatics analysis. Furthermore, gene expression data enables investigation of synthetic lethal pathways and graph structure of synthetic lethal genes within them.

Approach

A computational methodology, the Synthetic Lethal Prediction Tool ([SLIPT](#)) has been developed to detect synthetic lethal interactions in gene expression data. This methodology was demonstrated on interactions with *CDH1* in breast and stomach cancer data from The Cancer Genome Atlas ([TCGA](#)) project. Synthetic lethal genes and pathways were further investigated with unsupervised clustering, gene set over-representation analysis, metagenes, and permutation resampling. In particular, analyses focused on comparing [SLIPT](#) gene candidates to an experimental [siRNA](#) screen [Telford *et al.* \(2015\)](#). Network analysis methods were applied to the most supported pathways to test for pathway structure among between synthetic lethal candidates. Simulation and modelling was used to assess the statistical performance of [SLIPT](#), including simulated data with correlation structures derived from graph structures.

Findings

Many candidate synthetic lethal partners of *CDH1* were detected in both [TCGA](#) breast cancer. These genes clustered into several distinct groups, with distinct biological functions and elevated expression in different clinical subtypes. While the number of genes detected by both approaches was not significant, these contained significantly enriched pathways. In particular, $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting were robustly supported by both approaches, which is consistent with the known cytoskeletal and cell signalling roles of [E-cadherin](#) and validation of [GPCR](#) pathways performed by [Telford *et al.* \(2015\)](#). Many of these pathways were replicated in stomach cancer data. The pathways supported only by [SLIPT](#) included regulation of immune signalling and translational elongation which were not expected to be detected in an isogenic cell line model but are still candidates for further investigation.

Synthetic lethal candidates detected by [SLIPT](#) and [siRNA](#) were compared within graph structures of the candidate synthetic lethal pathways. These genes did not differ with respect to network metrics of importance or connectivity in the pathway. There was little support, across pathways, that [SLIPT](#) gene candidates were consistently upstream or downstream of [siRNA](#) gene candidates within pathways.

A model of synthetic lethality was used to simulate gene expression data with synthetic lethal partners of a gene. The [SLIPT](#) methodology had high statistical performance, detecting few synthetic lethal partners, which diminished with more synthetic lethal partners or lower sample size. The [SLIPT](#) methodology performed better than Pearson correlation or the χ^2 -test. In particular, it performed well with high specificity for datasets containing thousands of genes or genes positively correlated with the query gene (as expected to occur in expression data). [SLIPT](#) was robust across correlation structures, including those derived from complex pathway structures and often distinguished synthetic lethal genes from those positively or negatively correlated with them. Therefore [SLIPT](#) is appropriate to identify synthetic lethal genes within pathways and use candidate synthetic lethal genes (and their correlates) to identify synthetic lethal pathways.

Summary

Thus this thesis has developed, evaluated, and refined a bioinformatics approach to discovery of synthetic lethal genes solely from gene expression data. This approach has been demonstrated to detect biologically informative and clinically relevant candidate partners for *CDH1* in breast and stomach cancers. These investigations have also involved the development of network analysis and simulation procedures which may be more widely applicable.

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どうもありがとう由ちゃん。頑張った!もうすぐ行きます。!また来月!

Contents

Glossary	xvii
Acronyms	xxiv
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	3
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomic Data	5
1.1.3 Genomics Projects	5
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	6
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	8
1.1.4.2 Precision Cancer Medicine	9
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	9
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.2 Synthetic Lethal Cancer Medicine	12
1.2.1 Synthetic Lethal Genetic Interactions	13
1.2.2 Synthetic Lethal Concepts in Genetics	13
1.2.3 Synthetic Lethality in Model Systems	15
1.2.3.1 Synthetic Lethal Pathways and Networks	15
1.2.3.2 Evolution of Synthetic Lethality	16
1.2.4 Synthetic Lethality in Cancer	17
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	18
1.2.6 High-throughput Screening for Synthetic Lethality	20
1.2.6.1 Synthetic Lethal Screens	21
1.2.7 Computational Prediction of Synthetic Lethality	22
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	22
1.2.7.2 Comparative Genomics	23
1.2.7.3 Analysis and Modelling of Protein Data	26
1.2.7.4 Differential Gene Expression	28
1.2.7.5 Data Mining and Machine Learning	29

1.2.7.6	Mutual Exclusivity and Bimodality	32
1.2.7.7	Rationale for Further Development	33
1.3	E-cadherin as a Synthetic Lethal Target	33
1.3.1	The <i>CDH1</i> gene and its Biological Functions	34
1.3.1.1	Cytoskeleton	34
1.3.1.2	Extracellular and Tumour Micro-environment	34
1.3.1.3	Cell-Cell Adhesion and Signalling	35
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	35
1.3.2.1	Breast Cancers and Invasion	35
1.3.3	Hereditary Diffuse Gastric (and Lobular Breast) Cancer	36
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	37
1.4	Summary and Research Direction of Thesis	38
1.4.1	Thesis Aims	39
2	Methods and Resources	41
2.1	Bioinformatics Resources for Genomics Research	41
2.1.1	Public Data and Software Packages	41
2.1.1.1	Cancer Genome Atlas Data	42
2.1.1.2	Reactome and Annotation Data	43
2.2	Data Handling	43
2.2.1	Normalisation	43
2.2.2	Sample Triage	43
2.2.3	Metagenes and the Singular Value Decomposition	44
2.2.4	Candidate Triage and Integration with Screen Data	46
2.3	Techniques	46
2.3.1	Statistical Procedures and Tests	47
2.3.2	Gene Set Over-representation Analysis	48
2.3.3	Clustering	48
2.3.4	Heatmap	48
2.3.5	Modelling and Simulations	49
2.3.5.1	Receiver Operating Characteristic Curves	50
2.3.6	Resampling Analysis	50
2.4	Pathway Structure Methods	51
2.4.1	Network and Graph Analysis	51
2.4.2	Sourcing Graph Structure Data	52
2.4.3	Constructing Pathway Subgraphs	52
2.4.4	Network Analysis Metrics	53
2.5	Implementation	54
2.5.1	Computational Resources and Linux Utilities	54
2.5.2	R Language and Packages	55
2.5.3	High Performance and Parallel Computing	58
3	Methods Developed During Thesis	60
3.1	A Synthetic Lethal Detection Methodology	60
3.2	Synthetic Lethal Simulation and Modelling	62
3.2.1	A Model of Synthetic Lethality in Expression Data	63

3.2.2	Simulation Procedure	67
3.3	Detecting Simulated Synthetic Lethal Partners	70
3.3.1	Binomial Simulation of Synthetic Lethality	70
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	72
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	74
3.3.2.2	Specificity with Query-Correlated Pathways	80
3.4	Graph Structure Methods	84
3.4.1	Upstream and Downstream Gene Detection	84
3.4.1.1	Permutation Analysis for Statistical Significance	85
3.4.2	Simulating Gene Expression from Graph Structures	85
3.5	Customised Functions and Packages Developed	90
3.5.1	Synthetic Lethal Interaction Prediction Tool	90
3.5.2	Data Visualisation	91
3.5.3	Extensions to the iGraph Package	91
3.5.3.1	Sampling Simulated Data from Graph Structures	93
3.5.3.2	Plotting Directed Graph Structures	93
3.5.3.3	Computing Information Centrality	94
3.5.3.4	Testing Pathway Structure with Permutation Testing	94
3.5.3.5	Metapackage to Install iGraph Functions	95
4	Synthetic Lethal Analysis of Gene Expression Data	96
4.1	Synthetic Lethal Genes in Breast Cancer	97
4.1.1	Synthetic Lethal Pathways in Breast Cancer	98
4.1.2	Expression Profiles of Synthetic Lethal Partners	100
4.1.2.1	Subgroup Pathway Analysis	103
4.2	Comparing Synthetic Lethal Gene Candidates	105
4.2.1	Primary siRNA Screen Candidates	105
4.2.2	Comparison with Correlation	105
4.2.3	Comparison with Primary Screen Viability	108
4.2.4	Comparison with Secondary siRNA Screen Validation	110
4.2.5	Comparison to Primary Screen at Pathway Level	111
4.2.5.1	Resampling Genes for Pathway Enrichment	113
4.2.6	Integrating Synthetic Lethal Pathways and Screens	118
4.3	Synthetic Lethal Pathway Metagenes	119
4.4	Replication in Stomach Cancer	121
4.5	Discussion	122
4.5.1	Strengths of the SLIPT Methodology	122
4.5.2	Synthetic Lethal Pathways for E-cadherin	123
4.5.3	Replication and Validation	125
4.5.3.1	Integration with siRNA Screening	125
4.5.3.2	Replication across Tissues	126
4.6	Summary	126

5	Synthetic Lethal Pathway Structure	128
5.1	Synthetic Lethal Genes in Reactome Pathways	128
5.1.1	The PI3K/AKT Pathway	129
5.1.2	The Extracellular Matrix	131
5.1.3	G Protein Coupled Receptors	134
5.1.4	Gene Regulation and Translation	134
5.2	Network Analysis of Synthetic Lethal Genes	136
5.2.1	Gene Connectivity and Vertex Degree	137
5.2.2	Gene Importance and Centrality	138
	5.2.2.1 Information Centrality	138
	5.2.2.2 PageRank Centrality	140
5.3	Relationships between Synthetic Lethal Genes	141
5.3.1	Detecting Upstream or Downstream Synthetic Lethality	142
5.3.2	Resampling for Synthetic Lethal Pathway Structure	144
5.4	Discussion	146
5.5	Summary	148
6	Simulation and Modelling of Synthetic Lethal Pathways	149
6.1	Synthetic Lethal Detection Methods	150
6.1.1	Performance of SLIPT and χ^2 across Quantiles	151
	6.1.1.1 Correlated Query Genes affects Specificity	154
6.1.2	Alternative Synthetic Lethal Detection Strategies	156
	6.1.2.1 Correlation for Synthetic Lethal Detection	157
	6.1.2.2 Testing for Bimodality with BiSEp	158
6.2	Simulations with Graph Structures	159
6.2.1	Performance over Graph Structures	160
	6.2.1.1 Simple Graph Structures	160
	6.2.1.2 Constructed Graph Structures	163
6.2.2	Performance with Inhibitions	165
6.2.3	Synthetic Lethality across Graph Structures	171
6.2.4	Performance within a Simulated Human Genome	174
6.3	Simulations in More Complex Graph Structures	179
6.3.1	Simulations over Pathway-based Graphs	180
6.3.2	Pathway Structures in a Simulated Human Genome	182
6.4	Discussion	185
	6.4.1 Simulation Procedure	185
	6.4.2 Comparing Methods with Simulated Data	186
	6.4.3 Design and Performance of SLIPT	187
	6.4.4 Simulations from Graph Structures	189
6.5	Summary	190
7	Discussion	192
7.1	Synthetic Lethality and <i>CDH1</i> Biology	192
	7.1.1 Established Functions of <i>CDH1</i>	193
	7.1.2 The Molecular Role of <i>CDH1</i> in Cancer	193
7.2	Significance	194

7.2.1	Synthetic Lethality in the Genomic Era	194
7.2.2	Clinical Interventions based on Synthetic Lethality	196
7.3	Future Directions	197
7.4	Conclusions	199
	Bibliography	201
A	Sample Quality	225
A.1	Sample Correlation	225
A.2	Replicate Samples in TCGA Breast Cancer Data	228
B	Software Used for Thesis	232
C	Mutation Analysis in Breast Cancer	241
C.1	Synthetic Lethal Genes and Pathways	241
C.2	Synthetic Lethal Expression Profiles	242
C.3	Comparison to Primary Screen	245
C.3.1	Resampling Analysis	247
C.4	Compare SLIPT genes	249
D	Metagene Analysis	251
D.1	Pathway Signature Expression	251
D.2	Synthetic Lethal Reactome Metagenes	255
E	Intrinsic Subtyping	256
F	Stomach Expression Analysis	258
F.1	Synthetic Lethal Genes and Pathways	258
F.2	Comparison to Primary Screen	262
F.2.1	Resampling Analysis	264
F.3	Metagene Analysis	266
G	Synthetic Lethal Genes in Pathways	267
H	Network Analysis for Mutation SLIPT	274
I	Pathway Structure for Mutation SLIPT	277
J	Performance of SLIPT and χ^2	279
J.1	Correlated Query Genes affects Specificity	285
K	Simulations on Graph Structures	291
K.0.1	Simulations from Inhibiting Graph Structures	292
K.1	Simulation across Graph Structures	295
K.2	Simulations from Complex Graph Structures	299
K.2.1	Simulations from Complex Inhibiting Graphs	302
K.3	Simulations from Pathway Graph Structures	308

List of Tables

1.1	Methods for predicting genetic interactions	23
1.2	Methods for predicting synthetic lethality in cancer	24
1.3	Methods used by Wu <i>et al.</i> (2014)	25
2.1	Excluded samples by batch and clinical characteristics.	44
2.2	Computers used during thesis	54
2.3	Linux utilities and applications used during thesis	55
2.4	R installations used during thesis	56
2.5	R Packages used during thesis	56
2.6	R packages developed during thesis	58
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	98
4.2	Pathways for <i>CDH1</i> partners from SLIPT	99
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT	104
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i>	107
4.5	Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary short interfering RNA (siRNA) screen	111
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	112
4.7	Pathways for <i>CDH1</i> partners from SLIPT	115
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen .	116
4.9	Examples of candidate metagenes synthetic lethal for <i>CDH1</i> from SLIPT	120
5.1	ANOVA for synthetic lethality and vertex degree	138
5.2	ANOVA for synthetic lethality and information centrality	139
5.3	ANOVA for synthetic lethality and PageRank centrality	140
5.4	Resampling for pathway structure of synthetic lethal detection methods	145
B.1	Complete list of R packages used during this thesis	232
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT . . .	241
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	242
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	244
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	246
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	247
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	248
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . .	255

E.1	Comparison of intrinsic subtypes	256
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	258
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	259
F.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT	261
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	263
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	264
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	265
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	266
H.1	ANOVA for synthetic lethality and vertex degree	276
H.2	ANOVA for synthetic lethality and information centrality	276
H.3	ANOVA for synthetic lethality and PageRank centrality	276
I.1	Resampling for pathway structure of synthetic lethal detection methods	278

List of Figures

1.1	Synthetic genetic interactions	14
1.2	Synthetic lethality in cancer	17
2.1	Read count density	45
2.2	Read count sample mean	45
3.1	Framework for synthetic lethal prediction	61
3.2	Synthetic lethal prediction adapted for mutation	62
3.3	A model of synthetic lethal gene expression	64
3.4	Modelling synthetic lethal gene expression	65
3.5	Synthetic lethality with multiple genes	66
3.6	Simulating gene function	68
3.7	Simulating synthetic lethal gene function	68
3.8	Simulating synthetic lethal gene expression	69
3.9	Performance of binomial simulations	71
3.10	Comparison of statistical performance	71
3.11	Performance of multivariate normal simulations	73
3.12	Simulating expression with correlated gene blocks	75
3.13	Simulating expression with correlated gene blocks	76
3.14	Synthetic lethal prediction across simulations	78
3.15	Performance with correlations	79
3.16	Comparison of statistical performance with correlation structure	80
3.17	Performance with query correlations	81
3.18	Statistical evaluation of directional criteria	82
3.19	Performance of directional criteria	83
3.20	Simulated graph structures	86
3.21	Simulating expression from a graph structure	87
3.22	Simulating expression from graph structure with inhibitions	88
3.23	Demonstration of violin plots with custom features	92
3.24	Demonstration of annotated heatmap	92
3.25	Simulating graph structures	94
4.1	Synthetic lethal expression profiles of analysed samples	101
4.2	Comparison of SLIPT with siRNA	106
4.3	Comparison of SLIPT and siRNA genes with correlation	106
4.4	Comparison of SLIPT and siRNA genes with correlation	108
4.5	Comparison of SLIPT and siRNA genes with screen viability	109

4.6	Comparison of SLIPT genes with siRNA screen viability	109
4.7	Resampled intersection of SLIPT and siRNA candidate genes	114
5.1	Synthetic lethality in the PI3K cascade	130
5.2	Synthetic lethality in Elastic Fibre Formation	132
5.3	Synthetic lethality in Fibrin Clot Formation	133
5.4	Synthetic lethality in the GPCRs	135
5.5	Synthetic lethality and vertex degree	137
5.6	Synthetic lethality and centrality	139
5.7	Synthetic lethality and PageRank	141
5.8	Structure of synthetic lethality resampling	143
6.1	Performance of χ^2 and SLIPT across quantiles	152
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	153
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation	154
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	155
6.5	Performance of negative correlation and SLIPT	158
6.6	Simple graph structures	161
6.7	Performance of simulations on a simple graph	162
6.8	Performance of simulations is similar in simple graphs	163
6.9	Performance of simulations on a pathway	164
6.10	Performance of simulations on a simple graph with inhibition	166
6.11	Performance is higher on a simple inhibiting graph	168
6.12	Performance of simulations on a constructed graph with inhibition	169
6.13	Performance is affected by inhibition in graphs	170
6.14	Detection of synthetic lethality within a graph structure	172
6.15	Performance of simulations including a simple graph	176
6.16	Performance on a simple graph improves with more genes	177
6.17	Performance on an inhibiting graph improves with more genes	178
6.18	Performance of simulations on the PI3K cascade	181
6.19	Performance of simulations including the PI3K cascade	183
6.20	Performance on pathways improves with more genes	184
A.1	Correlation profiles of removed samples	226
A.2	Correlation analysis and sample removal	227
A.3	Replicate excluded samples	228
A.4	Replicate samples with all remaining	229
A.5	Replicate samples with some excluded	230
C.1	Synthetic lethal expression profiles of analysed samples	243
C.2	Comparison of mtSLIPT to siRNA	245
C.3	Compare mtSLIPT and siRNA genes with correlation	249
C.4	Compare mtSLIPT and siRNA genes with correlation	249
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	250
D.1	Pathway metagene expression profiles	253

D.2	Expression profiles for estrogen receptor related genes	254
F.1	Synthetic lethal expression profiles of stomach samples	260
F.2	Comparison of SLIPT in stomach to siRNA	262
G.1	Synthetic lethality in the PI3K/AKT pathway	267
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer	268
G.3	Synthetic lethality in the Extracellular Matrix	269
G.4	Synthetic lethality in the GPCR Downstream	270
G.5	Synthetic lethality in the Translation Elongation	271
G.6	Synthetic lethality in the Nonsense-mediated Decay	272
G.7	Synthetic lethality in the 3' UTR	273
H.1	Synthetic lethality and vertex degree	274
H.2	Synthetic lethality and centrality	275
H.3	Synthetic lethality and PageRank	275
I.1	Structure of synthetic lethality resampling	277
J.1	Performance of χ^2 and SLIPT across quantiles	279
J.2	Performance of χ^2 and SLIPT across quantiles	281
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	283
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation	285
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation	287
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	289
K.1	Performance of simulations on a simple graph	291
K.2	Performance of simulations on an inhibiting graph	292
K.3	Performance of simulations on a constructed graph with inhibition	293
K.4	Performance of simulations on a constructed graph with inhibition	294
K.5	Detection of synthetic lethality within a graph structure	295
K.6	Detection of synthetic lethality within an inhibiting graph	297
K.7	Detection of synthetic lethality within an inhibiting graph	298
K.8	Performance of simulations on a branching graph	299
K.9	Performance of simulations on a complex graph	300
K.10	Performance of simulations on a large graph	301
K.11	Performance of simulations on a branching graph with inhibition	302
K.12	Performance of simulations on a branching graph with inhibition	303
K.13	Performance of simulations on a complex graph with inhibition	304
K.14	Performance of simulations on a complex graph with inhibition	305
K.15	Performance of simulations on a large constructed graph with inhibition	306
K.16	Performance of simulations on a large constructed graph with inhibition	307
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	308
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	309

Glossary

allele	A gene variant with a specific sequence and phenotype.
bioinformatics	Statistical or computational approaches to biological data or research tools.
bisulfite-Seq	Epigenomic data from sequencing bisulfite treated DNA.
CAGE-Seq	Transcriptome data from cap analysis of gene expression.
cancer	A class of diseases, formally “malignant neoplasm”, of abnormal cellular growth and spread to other organs.
cancer gene	A gene which is involved in the malignancy of some cancers, encompassing oncogenes and tumour suppressors , which have molecular aberrations in cancer or variants which predispose individuals to cancer.
centrality	A network metric which identifies important vertices .
chemoprevention	The use of drugs to prevent early-stage cancers, generally applied to high-risk mutation carriers.
chemotherapy	The use of cytotoxic drugs to treat cancers, in combinations, generally applied to advanced stage cancers.
ChIP-Seq	Epigenome data from chromatin immunoprecipitation sequencing.
compound screen	A high-throughput screen performed using a library of chemical compounds.
computational biology	Applying computational or mathematical modelling to understanding biological systems and relationships.

conditional essentiality	A gene becoming essential to viability under certain environmental conditions, including presence of compounds which inactivate other genes.
copy number	The number of copies of DNA, typically two copies for diploid organisms but subject to variation.
<i>de novo</i>	A bioinformatics sequence assembly conducted entirely from raw genomics data without a reference sequence.
diagnosis	The identification of disease by clinical, cellular, and molecular characteristics.
driver mutation	A mutation which promotes cancer growth.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
edge or link	A relationship connecting a pair of elements of a graph structure or network, may be weighted or directional.
epigenome	An analysis of epigenetic modifications of all genes in the genome.
epistasis (biological)	The effects of a gene modifying or masking the phenotype of another gene.
epistasis (statistical)	A divergence of the observed double mutant phenotype from that expected based on the respective phenotypes of single mutant (Fisher, 1919).
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
exome	A sequencing approach designed to generate data enriched for coding genes within the genome.
familial	A trait recurrently occurring in families, not necessarily with a genetic cause.
functional redundancy	Genes which perform a common function, also known as genetic redundancy.

gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
genetic robustness	A system of biological pathways which (has evolved to) continue to function as a whole under various conditions, including the inactivation of various individual genes.
genome	All of the DNA sequence in the genome.
genomic	The use of data from all genes in the genome.
genomic medicine	The use of genomic information to tailor medicine treatment to the genetics of an individual.
germline mutation	A mutation that occurred in germline cells and is passed between generation.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
hallmark of cancer	An underlying characteristic of cancer as part of a rational approach devised by (Hanahan and Weinberg, 2000).
hereditary	A trait or disease which has a genetic cause and is inherited from family members.
high-throughput screen	An experimental procedure to perform a large scale series of chemical, genetic, or pharmacological tests.
hub	A central or highly connected component of a network.
<i>in silico</i>	An investigation conducted using computations, typically simulations or analyses.
<i>in vitro</i>	An investigation conducted using a controlled experimental system to examine biomolecules.
<i>in vivo</i>	An investigation conducted using in the context of a biological cell or organism, including pre-clinical models and clinical trials.
induced essentiality	A gene becoming essential to viability under certain conditions, including inactivation of a synthetic lethal partner.
information centrality	A network centrality metric which uses the impact of removing a vertex or node on connections in the network.

intrinsic subtype	Distinguishing cancer by molecular and genetic features.
MCF10A cell line	A non-tumorigenic epithelial cell line derived from breast tissue.
metabolome	All the metabolites and enzymes in the cell.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
metagenome	All of the genes and genomes in a community.
metastasis	A secondary growth of a tumour or spread of cancer to other organs.
methylation	A measure of the epigenetic regulation of DNA at CpG dinucleotide (CpG) sites.
microarray	A high-throughput technique to measure presence or abundance of nucleic acid sequences from binding to probes.
microRNA	Short RNA molecules generally regarded to regulate gene expression by binding to mRNA.
molecular profile	A combination of genetic and biochemical measures which identifies characteristic traits of a tumour.
molecular subtype	A classification of cancers based on an identification using molecular properties.
mutant	A variant or dysfunctional phenotype arising from a mutation in a gene.
mutation	A change in DNA sequence that disrupts gene function.
network biology	The application mathematical and computational approaches to networks in understanding biological relationships.
network medicine	The use of network biology to understand, prevent, or treat diseases.
non-oncogene addiction	The dependence of a cancer cell on functioning non-mutant genes.
'omics	A combination of approaches to generating biological data with high-throughput procedures such as genomics, proteomics or metabolomics.

oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
oncogene addiction	The dependence of a cancer cell on a specific oncogenic pathway.
PageRank centrality	A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
pan cancer	A focus on the molecular and genetic features across cancers in different tissues.
passenger mutation	A mutation that occurs in cancers but does not affect the growth of cancers.
pathway	A series of biomolecules that produces a particular product or biological function.
pleiotropy	When a gene has multiple biological functions.
polypharmacology	The design of drugs to target multiple molecular targets or biological pathways.
precision medicine	The application of prevention and treatment measures to target diseases by molecular and genetic features.
prognosis	The estimation of disease progression and patient outcome.
proteome	All the proteins expressed from the genome.
proto-oncogene	The non-mutant variant or precursor to a mutant oncogene .
recurrent mutation	The repeated occurrence of mutations in a particular gene across cancers.
RNAi screen	A high-throughput screen performed using a RNA interference (RNAi) .
RNA-Seq	The generation of transcriptome data from sequencing RNA.
Sanger sequencing	A dideoxy chain termination method for DNA sequencing (named after Fred Sanger).
scale-free	A property of a network which has a power law vertex degree distribution, that is several highly connected hub genes and many with very few connections.

shortest path	A path with the fewest possible edges which connects two particular vertices .
small world	A property of a network which is highly connected and has a low characteristic path length, derived from the mean shortest path length across all pairs of nodes.
somatic mutation	A mutation that occurs in somatic cells, during a patient's lifespan.
sporadic cancer	Cancers which do occur in patients with a family history or carry a high-risk genetic variant.
synergy	When multiple drugs have more effect than expected from the effect of each separately.
synthetic dosage lethal	A synthetic genetic interaction (SGI) analogous to synthetic lethality where where one gene is inactivated and the other over-expressed.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
synthetic lethal screen	A high-throughput screen performed on isogenic cell lines to detect genes for which inhibition specifically deleterious to the null mutant genotype.
synthetic rescue	A synthetic genetic interaction when the combined mutations restores the wild-type the phenotype of one of the mutations .
synthetic sick	Genetic interactions where inactivation of multiple genes is deleterious which are viable if inactivated separately.
synthetic suppression	A synthetic genetic interaction when the combined mutations (partially) suppresses the mutant phenotype of one of the mutations .
targeted therapy	Cancer treatment that specifically acts against a molecular target, in contrast to standard chemotherapy.
transcriptome	All of the genes expressed in the genome.
treatment	Medical procedures for a disease to improve patient outcomes.
tumour	An abnormal lump of tissue or growth of cells, may be cancerous.

tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.
vertex degree	A network metric of connectivity of vertices which uses the number of edges connected to each vertex or node .
vertex or node	An element of a graph structure or network.
wild-type	A natural phenotype of a trait or the normally functional allele which encodes it.

Acronyms

1KGP	1000 genomes project.
ADP	Adenosine Diphosphate.
AMP	Adenosine Monophosphate.
AMPK	AMP -activated Protein Kinase.
ANOVA	Analysis of Variance.
ATP	Adenosine Triphosphate.
AUROC	Area Under the Receiver Operating Characteristic (curve).
Bash	Bourne Again Shell.
BioPAX	Biological Pathway Exchange.
BiSep	Bimodal Subsetting Expression.
BMP	Bone Morphogenic Protein.
cAMP	Cyclic AMP .
CCL	Cancer Cell Line Encyclopaedia.
cDNA	Complementary DNA (from mRNA).
CGP	Cancer Genome Project.
ChIP	Chromatin Immunoprecipitation.
ChIP-Seq	Chromatin Immunoprecipitation Sequencing.
CNV	Copy Number Variation.
COSMIC	Catalogue Of Somatic Mutations In Cancer.
CpG	5'-C-phosphate-G-3'.
CPM	Counts Per Million mapped reads.
CPU	Central Processing Unit.
CRAN	comprehensive R archive network.
CXCR	Chemokine Receptor.
DAISY	Data Mining Synthetic Lethal Identification Pipeline.
DDBJ	DNA Data Bank of Japan.
DNA	Deoxyribonucleic Acid.
EMBL	European Molecular Biology Laboratory.

EMT	Epithelial-Mesenchymal Transition.
ENA	The European Nucleotide Archive.
ENCODE	Encyclopaedia of DNA Elements.
ER	Estrogen Receptor.
exprSL	Synthetic Lethality (expression).
FANTOM	Functional Annotation Of Mammalian genome.
FDR	False Discovery Rate.
GEO	Gene Expression Omnibus.
GO	Gene Ontology.
GPCR	G Protein Coupled Receptor.
HDAC	Histone Deacetylase.
HDGC	Hereditary Diffuse Gastric Cancer.
HLRCC	Hereditary Leiomyomatosis and Renal Cell Carcinoma.
HPC	High Performance Computing.
ICGC	International Cancer Genome Consortium.
IHC	Immunohistochemistry.
InDel	Insertion or Deletion (in DNA sequence).
JAK	Janus Kinase.
lncRNA	Long Non-Coding RNA.
METABRIC	Molecular Taxonomy of Breast Cancer International Consortium.
microRNA	Micro RNA.
mRNA	Messenger RNA.
MSI	Microsatellite Instability.
mtSL	synthetic Lethality (mutation).
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NCBI	National Center for Biotechnology Information (in the USA).
NCI	National Cancer Institute (in the USA).
NeSI	New Zealand eScience Infrastructure.

NGS	Next-Generation Sequencing.
NHGRI	National Human Genome Research Institute (in the USA).
NIG	National Institute of Genetics (in Japan).
NIH	National Institutes of Health (in the USA).
NMD	Nonsense-Mediated Decay.
PAM50	Prediction Analysis of Microarray 50.
PARP	Poly-ADP-Ribose Polymerase.
PCR	Polymerase Chain Reaction.
PDE	Phosphodiesterase.
PI3K	Phosphoinositide 3-kinase.
PIP ₂	Phosphatidylinositol-(4,5)-bisphosphate.
PIP ₃	Phosphatidylinositol-(3,4,5)-trisphosphate.
PPI	Protein-Protein Interaction.
PR	Progesterone Receptor.
qPCR	Quantitative (real-time) Polymerase Chain Reaction.
RFLP	Restriction Fragment Length Polymorphism.
RGS	G-protein Signalling.
RHO	Ras Homolog Family.
RMA	Robust Multiarray Averaging (normalisation.
RNA	Ribonucleic Acid.
RNAi	RNA Interference.
ROC	Receiver Operating Characteristic (curve).
RPKM	Reads Per Kilobase per Million mapped reads.
RPPA	Reverse Phase Protein Arrays.
RRBS	Reduced Representation Bisulfite Sequencing.
rRNA	Ribonucleic acid.
RSEM	RNA-Seq by Expectation Maximization (normalisation.
SGA	Synthetic Gene Array (technique).
SGI	Synthetic Genetic Interaction.
shRNA	Short Hairpin RNA.
siRNA	Short Interfering RNA.
SL	Synthetic Lethal.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
Slurm	Simple Linux Utility for Resource Management.

SNP	Single Nucleotide Polymorphism.
SOCKS	Socket Secure.
SR	Synthetic Rescue (or viability).
SS	Synthetic Suppression.
SSL	Synthetic Sick.
TCGA	The Cancer Genome Atlas (genomics project).
TGF α	Transforming Growth Factor α .
TMM	Trimmed Mean of M values (normalisation.
tRNA	Transfer RNA.
UCSC	University of California, Santa Cruz.
UTR	Untranslated Region (of mRNA).
WNT	Wingless-Related Integration Site.

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