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REVIEW

Translational genomics in cancer research: converting profiles into personalized cancer medicine

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ABSTRACT Cancer genomics is a rapidly growing discipline in which the genetic molecular basis of malignancy is studied at the scale of whole genomes. While the discipline has been successful with respect to identifying specific oncogenes and tumor suppressors involved in oncogenesis, it is also challenging our approach to managing patients suffering from this deadly disease. Specifically cancer genomics is driving clinical oncology to take a more molecular approach to diagnosis, prognostication, and treatment selection. We review here recent work undertaken in cancer genomics with an emphasis on translation of genomic findings. Finally, we discuss scientific challenges and research opportunities emerging from findings derived through analysis of tumors with high-depth sequencing.

KEY WORDS Cancer; genomics; translation; personalized medicine

Introduction

Sun Tzu stated in The Art of War, "If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle."

These words have held true with respect to the efforts of medical science to conquer cancer as a cause of death and suffering. There have been both occasions when the drivers of malignancy eluded curative efforts and also occasions when our diagnostic and therapeutic strategies have not met the task despite the underlying molecular biology of disease becoming more evident. Translational cancer research has accordingly benefited from both advances in our understanding of the enemy that cancer continues to be and the ongoing effort to evaluate and make better the suite of diagnostics, therapeutics, and rational decision making that underlie cancer treatment.

More than a decade into the post-genomic era, we have come to appreciate human malignancy as a condition derived from somatic aberrations in the human genome. Early studies enabled by oligonucleotide hybridization arrays proved to be highly informative, demonstrating a role for somatic copy number variations (CNVs)[1], mutations[2], and differential transcript expression[3] as cancer promoting events. Current efforts build from these successes while benefiting from the rapid evolution of high throughput sequencing and bioinformatics techniques[4]. To this end, several coordinated multi-center efforts including The Cancer Genome Atlas (TCGA)[5] and the International Cancer Genome Consortium (ICGC)[6] have been organized to interrogate the genomes of dozens of cancer types. Several cancer genome sequencing studies have also been reported by independent groups[7-11]. Reviewed here are emerging themes from these studies and their applications to both the biology of cancer and new concepts in patient management.

Molecular subtyping through integrative analysis

The cost of microarrays and high-throughput sequencing lends

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itself to the development of multiple molecular profiles per cancer type. For instance, gene expression, somatic mutation calls, and DNA copy number can each be assessed in a sample matched manner on large cohorts of clinical specimens. When such profiles are coupled with drug response and clinical outcomes annotation, integrative analysis can be performed to reveal clinically relevant molecular subsets. Early efforts demonstrated the value of genomic data integration using the NCI60 panel of cell lines to predict therapeutic response[12,13]. Recent work by the Cancer Cell Line Encyclopedia[14] and Genomics of Drug Sensitivity in Cancer[15] expanded this effort to include a larger panel of cell lines with more thorough genomic profiling, and has provided a suite of molecular diagnostics that may help better match patients to targeted therapies to which they respond.

Although efforts utilizing cell lines have proven to be informative, the most informative analysis would be of profiles generated from clinical cases. Genomic and clinicopathologic profiles made public by the TCGA provide a unique opportunity to decipher the molecular basis of the heterogeneity in clinical course taken by single diseases and in some cases reveal unexpected associations in molecular etiology across diseases. For instance, analysis by the TCGA of high grade serous ovarian cancer (OvCa) identified four distinct gene expression clusters: differentiated, immunoreactive, proliferative, and mesenchymal[16]. The same study also identified microRNA expression clusters C1, C2, and C3 of which microRNA cluster C1 associates with cases bearing a proliferative gene expression profile and C2 associates with messenchymal cases. Further interrogation by the TCGA determined that the C1 microRNA signature predicts diminished survival. Together these data suggest that microRNA networks define a significant regulatory mechanism and may distinguish actionable subtypes of clinical cases.

Pursuant to these findings, Yang *et al.*[17] developed a computational pipeline (Master mIRna Analysis for Cancer moLecular subtype, MIRACLE) which aims to delineate the driver events and applied them to identify driver miRNAs for the mesenchymal signature of ovarian cancer. Using genes in the regulatory network, the study further characterized an integrated mesenchymal subtype significantly associated with poor survival in 459 serous OvCa cases from TCGA and 560 cases from three independent OvCa patient cohorts. The miRNA-regulatory network derived from this analysis consists of eight key miRNAs predicted to regulate 89% of the targets. Among them are not only well-established EMT inhibitors such as miR-200 family but also previously uncharacterized drivers such as miR-506 which Yang *et al.*[17] demonstrated to be a novel EMT inhibitor by targeting SNAI2. Specifically, transfection of miR-506 augmented E-cadherin expression, inhibited cell migration and invasion, and prevented TGFβ-induced EMT, while force expression of SNAI2 abolished miR-506's effect. In human samples, miR-506 expression correlated with decreased SNAI2, elevated E-cadherin, and beneficial prognosis. Exploring the therapeutic efficacy of miR-506 in OvCa, the study also demonstrated the suppression of EMT and tumor growth *in vivo* subsequent to treatment with nanoparticle-incorporated miR-506 in orthotopic OvCa mouse models. Integrative genomic analysis in this study has thus nominated miR-506 as both a prognostic marker and potential therapeutic indicator.

Similarly, the application Mutually Exclusive Modules in Cancer (MEMo), an integrative analysis pipeline leveraging correlation analysis and graph theory, was deployed using data from the TCGA to characterize networks in glioblastoma multiforme (GBM). In doing so, two regulatory networks were identified by a total of six genes, distilling out a small subset of putative drivers from hundreds of genetic events[18]. The advantage of this analysis is not only that it limits the number of genes for functional follow-up studies probing the biology of GBM, but also that it nominates a workable six-gene panel for evaluation as a putative clinical diagnostic.

Other integrative tools have also been developed and applied for this purpose. The ARACNe algorithm recently uncovered regulatory interactions driving epithelial-to-mesenchymal transformation using the same GBM data as the MEMo study[19]. Likewise, PARADIGM, a pipeline that integrates genomic profiles into a model of transcriptional and cell-signaling interactions, inferred activation of the FOXM1 signaling as a highly recurrent high-grade serous OvCa[16]. While small-molecule inhibitors to transcription factors remain a challenge to develop, the capacity to identify cancers driven by specific transcription regulators may prove beneficial when identifying what subset of patients to treat with these drugs as they become available.

The inevitable consequence of generating enough data to observe the natural subsets occurring between samples of the same cancer is that efforts to treat cancer will necessarily evolve to be more subsets-specific. For instance, differentiated OvCa is likely to require a different therapeutic strategy from that of cases with a molecular signature that is more proliferative. Getting to the point where we know what strategy is best for each molecular subtype will require the same level of focused investigation within each molecular subtype as the studies that have led to their identification. Thus, a theme of molecular subtyping compelling more personalized treatment plans and more precise contexts for therapy development has emerged from cancer genome studies.

BRCA-driven ovarian cancer: a case of genomics driving personalization

In the general population, an estimated 1 in 300 to 800 individuals carries a BRCA1 or BRCA2 mutation[20]. And 8%-13% of women diagnosed with epithelial OvCa have a germline BRCA1 or BRCA2 mutation[21-23]. The mutation frequencies of BRCA1/2 raise to 16%-21% in serous subtype of ovarian cancer, which accounts for 70% of OvCa[21,23,24]. The risk of developing OvCa by age 70 years is 40%-50% for BRCA1 mutation carriers and 10%-20% for BRCA2 mutation carriers[25,26]. BRCA1 and BRCA2 mutations can be also found in primary fallopian tube and peritoneal cancers[27].

Accumulating evidence[28-31] shows that BRCA1/2 mutation-related OvCa cases have a discernibly diminished prognosis and platinum response rate compared to non-BRCA1/2 mutant OvCa cases. In a recent report, Yang and colleagues performed integrated analyses of multidimensional genomic and clinical data from 316 high-grade serous OvCa patients in TCGA project and observed that patients with BRCA1 and BRCA2 mutations had unequal clinical features[32]. Specifically, patients with BRCA1 mutations were younger at diagnosis and the 5-year survival rate of BRCA2 mutation carriers was significantly higher than that of wild-type cases. Among BRCA2 mutation carriers, 100% were sensitive to primary platinum chemotherapy compared with 80% of BRCA1-mutated and 85% of wild-type cases.

Similarly, patients with BRCA2 mutations had a longer platinum-free survival interval than did BRCA1-mutant and wild-type patients. The availability of genomic data profiling somatic mutations, DNA copy number alterations, and methylation in the TCGA for all the analyzed OvCa cases allowed the authors to evaluate molecular correlates in a quantitative manner. This analysis revealed that BRCA2 cases exhibited a more pronounced "mutator phenotype", as defined by the number of total mutations across the whole exome whereas BRCA1 mutated cancers exhibited no significant enrichment of mutations. Subsequent to this report, two independent studies also provided supporting evidence that BRCA2 mutation is associated with a better prognosis in OvCa[33,34], including a pooled observational study including 3,739 epithelial OvCa cases (909 BRCA1, 304 BRCA2 mutation carriers and 2,666 non-carriers), by Bolton *et al.*[33] reporting that BRCA2 mutation carriers had the best prognosis.

Since BRCA2 mutations are associated with longer platinum-free survival durations than are BRCA1 mutations and BRCA wild-type, a patient's BRCA status may influence the choice of agents for adjuvant chemotherapy. Recent findings[35,36] demonstrate that PARPi have cytotoxic effects on BRCA1- or BRCA2-deficient cells. The prevailing explanation for these findings center on a phenomenon called synthetic lethality[37]. Promising results from multiple clinical trials in BRCA-associated carcinomas, including OvCa, have been reported[38-41].

One important consideration is whether differentials in response to platinum-based chemotherapy between BRCA1- and BRCA2-mutated ovarian cancers observed in recent studies may also be true with respect to the therapeutic response elicited by PARP inhibitors. Early clinical trials of PARP inhibitors, although statistically underpowered at their current sample size to detect differences in efficacy between the BRCA gene mutations, demonstrate notable trends. A study by Gelmon *et al.*[41] included 11 BRCA1 and 5 BRCA2 mutated OvCa patients treated by PARPi and showed a 60% (3 of 5) response rate for BRCA2-mutant versus 24% (11of 60) for BRCA-wild-type and 36% (4 of 11) for BRCA1-mutant cases. A similar trend was shown in the cohort that received 400 mg of olaparib twice daily[39]. These marginal, but promising results indicate that further stratification based on BRCA1 and BRCA2 mutation status may be needed to evaluate the differential effects of PARPi treatment in individuals. In addition, upcoming trials of PARP inhibitors in ovarian cancer that specifically enrich for BRCA1 and BRCA2 carriers may be at particular risk for confounding biases in treatment response if differences in between these two biologically distinct groups are not considered.

Oncogenic gene fusions: a class of tumor defining genomic events

Originally associated with blood leukemias, fusion genes have become an emerging class of oncogenes in solid tumors. Fusion genes are two previously separate genes that rearrange forming a novel "hybrid" gene, containing both of the original genes. The first discovered and most widely characterized fusion gene, BCR-ABL1, occurs in 95% of chronic myeloid leukemia patients[42]. Since then, with the advent and commercial availability of next-generation sequencing, more fusions began to be discovered in solid tumors[43]. Next-generation sequencing allowed research groups to perform sequencing reactions rapidly and at a lower cost than previous reactions did. This greatly pushed efforts to sequencing a greater variety of tumor types, and thus lead to the identification and characterization of more fusions. These efforts collectively lead to development of drug inhibitors which have showed vast therapeutic benefit.

Fusion genes can form via translocations in which chromosomes exchange the location of entire chromosome arms, deletions in which a segment of DNA is deleted between two consecutive genes, inversions in which a segment of DNA

is inverted bringing two distant genes into the same open reading frame, or tandem duplications in which two genes in a region of microhomology are amplified and tiled next to one another. The TMPRSS2-ERG fusion is an example of a fusion forming via deletion, which results in the ERG gene put under the control of the androgen-regulated promoter *TMPRSS2*. This results in overexpression of the ERG oncogene leading to tumorigenesis[44]. The *FGFR3-TACC3* fusion gene found in GBM, bladder, and lung cancers, is an example of a fusion forming via tandem duplication. Both genes are amplified and tiled next to one another, leading to both genes occurring in the opposite direction as before the fusion event[45]. The BCR-ABL1 fusion is an example of translocation, in this case specifically between chromosomes 9 and 22[42].

Fusion genes are attractive as diagnostic tools and therapeutic targets. The first fusion gene to be targeted was *BCR-ABL1*, where the tyrosine kinase inhibitor, imatinib, targeted the constitutively activated ABL1 kinase, and was approved for use by the Food and Drug administration in 2001. Another targeted fusion, the *PML-RARA* fusion, which occurs in 95% of acute promyelocytic leukemia patients found vast therapeutic benefit when treated with drug tretinoin[46]. Futhermore, the FGFR family fusions, which recently have been discovered in a variety of cancers including breast[47], lung[47], GBM[48], and bladder cancers[49], are uniquely targetable due to overexpression of the tyrosine kinase FGFR. Future efforts are involved with discovering means to target these fusion genes in diverse cancers.

Fusion genes are oncogenic via a variety of different mechanisms, including constitutive activation or overexpression of an oncogene. As mentioned previously, the *BCR-ABL1* oncogene forms via reciprocal translocation and encodes a constitutive activated tyrosine kinase, ABL1. The addition of *BCR* to the *ABL1* gene allows for receptor dimerization and therefore constitutive activation, where the receptor is maintained within the cytoplasm where its signals continually propagates downstream signaling cascades[50,51]. Similarly, the *FGFR3-TACC3* fusion gene has been proposed to exert its oncogenic phenotype via constitutive dimerization[45,48,49]. Specifically, the tacc3 protein contains a coiled-coil domain in the C-terminal that is retained upon formation of the *FGFR3-TACC3* fusion. This coiled-coil domain is hypothesized to allow constitutive dimerization of the fusion, which then maintains activity even in the absence of ligand[47]. This can then lead to constitutive activation of known downstream oncogenes, such as ERK and STAT3[45,49]. Interestingly, other dimerization domains have been described in a variety of fusion genes, all which contain FGFR family members[47]. Exactly how these dimerization domains allow oncogenic FGFR signaling remains to be elucidated.

Another way that oncogenic fusions can be overexpressed is via loss of microRNA regulation. MicroRNAs (miRNAs) are small, endogenous RNA molecules that can lead to mRNA degradation or can inhibit translation. The miRNAs regulate specific mRNA when their seed sequence matches one within the 3' untranslated region (UTR) of a specific mRNA. Each miRNA has the potential to regulate hundreds of different mRNAs. The *FGFR3*-TACC3 fusion gene is one which can bypass microRNA regulation, via loss of the 3' untranslated region on FGFR3. Specifically, upon formation of the fusion the 3' UTR of FGFR3 lost. This 3' UTR is under tight control of the microRNA 99a (miR-99a), which is very high in normal brain and in GBM. This explains why there is little wild-type FGFR3 found in both normal brain and GBM. However, upon formation of the *FGFR3-TACC3* fusion, this mRNA is then able to bypass signaling and is overexpressed[45]. A similar mechanism is observed with the *MYB-NFIB* fusion in adenoid cystic carcinoma of the head and neck, which occurs via translocation of chromosomes 6 and 9. The *MYB* gene encodes the oncogenic Myb transcription factor, which is overexpressed in a variety of cancers. The 3' UTR of *MYB* is lost upon formation of the fusion, where it can then bypass microRNA signaling[52].

Yet another mechanism by which fusion genes can exert their oncogenic phenotype occurs when an oncogene comes under the control of another genes' more potent promoter. An example of this is the *TMPRSS2-ERG* fusion gene in prostate cancer. A segment between both genes is deleted which results in the *ERG* oncogene being in control of the *TMPRSS2* promoter. This promoter is androgen regulated, to where under normal conditions *TMPRSS2* is only expressed in prostate tissues when androgen is available. However, upon formation of the fusion, the *ERG* gene is therefore under control of this promoter, leading to the overexpression of ERG when androgen is present[44]. Similarly, another fusion gene found in prostate cancer links the SLC45A3 fusion to the same Ets family of transcription factors, although the prevalence is lower than *TMPRSS2-ERG* fusions[53]. A similar mechanism has recently been described linking the *SLC45A3* gene to *FGFR2*, where the *FGFR2* receptor tyrosine kinase is now under the control of the androgen regulated *SLC45A3*[47]. It is possible that TMPRSS2-fusion positive prostate cancer patients would uniquely responsive to androgen deprivation therapy, as this would limit the amount of androgen-induced oncogene being expressed. Given that many of these fusions are with genes that are members of the ETS-family, fusion-positive cases may also be uniquely served by inhibitors developed against this family of transcription factors. Patients with *SLC45A3-FGFR2* fusions may also benefit from FGFR inhibitor therapy to combat

oncogenic signaling conferred by *FGFR2* activity.

Future efforts towards targeted cancer therapy should include developing drugs with the potential to inhibit the gene-products of oncogenic fusions. However, given the fusion-specific nature of tumor-biology in lesions driven by gene-fusions, implementation of such treatments would be most effective when treating patients of known gene fusion status. In other words, drugging gene-fusions being an exercise in targeting individual cancers on the basis of patient-specific somatic events makes this class of targets naturally suited for personalized medicine.

Future directions and challenges: intra-tumoral heterogeneity and resistance

While the promise of more targeted precision therapy is hopeful, observations from clinical trails of targeted therapy demonstrate heterogeneity in treatment response even among lesions where drivers are known[54-57]. Innate and acquired resistance to targeted therapy accordingly presents a formidable challenge to translational efforts aimed at converting genomic findings into effective therapy. This has led some to parameterize treatment response using principles from evolutionary biology[58]. Specifically this view is predicated on the notion that tumors are heterogeneous populations of cancer cells that evolve through clonal and subclonal expansion to dynamically repopulate lesions under the selective pressure of systemic therapy. If this is true, then we may find the keys to unlocking durable treatment responses in the evolutionary behavior of tumors.

Only recently have genomic techniques capable of resolving intratumoral heterogeneity become available. Recent high-depth whole genome sequencing of lung cancers revealed the bi-clonal composition of tumors in both a smoker and a never smoker[59], lending support to notion that solid tumors can be heterogeneous. Similar high-depth sequencing of eight paired primary and replaced acute myeloid leukemia cases demonstrated that resistance to chemotherapy emerged, at least in this subset of cases representing a hematologic malignancy, through the expansion and evolution of subclones present in the primary setting[60].

Further advances in sequencing coupled with what we're learning from early tumor heterogeneity studies may help with designing rational regimens and combinations of treatment to overcome resistance and relapse. However, as we've learned from the genomic profiling across tumor cohorts, data in its pure form is not sufficient to address unmet needs. Instead it is the combination of well designed data collection with creative analytical approaches that lead to new and informative insights. Returning to the wisdom of Sun Tzu, since we have known that cancer is an enemy that uses genome editing to perpetually evolve, our pursuit of durable and curative therapeutic responses will require our treatment strategies to evolve more rapidly than our adversary. One strategy would be to slow tumor evolution down, an area of cancer biology we do not sufficiently understand at present to properly exploit and therefore need to study further. Another would be to become more dynamic therapists whose treatment plans for individual patients evolve to keep pace with the moving target individual lesions are showing themselves to be.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Davies JJ, Wilson IM, Lam WL. Array CGH technologies and their applications to Cancer genomes. Chromosome Res 2005;13:237-248.
2. Dutt A, Beroukhim R. Single nucleotide polymorphism array analysis of Cancer. Curr Opin Oncol 2007;19:43-49.
3. Schulze A, Downward J. Navigating gene expression using microarrays--a technology review. Nat Cell Biol 2001;3:E190-195.
4. Metzker ML. Sequencing technologies - the next generation. Nat Rev Genet 2010;11:31-46.
5. Collins FS, Barker AD. Mapping the cancer genome. Pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies. Sci Am 2007;296:50-57.
6. International Cancer Genome Consortium, Hudson TJ, Anderson W, Artez A, Barker AD, Bell C, et al. International network of cancer genome projects. Nature 2010;464:993-998.
7. Stephens PJ, Tarpey PS, Davies H, Van Loo P, Greenman C, Wedge DC, et al. The landscape of Cancer genes and mutational processes in breast cancer. Nature 2012;486:400-404.
8. Barbieri CE, Baca SC, Lawrence MS, Demichelis F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and Med12 mutations in prostate cancer. Nat Genet 2012;44:685-689.
9. Wei X, Walia V, Lin JC, Teer JK, Prickett TD, Gartner J, et al. Exome sequencing identifies GRIN2A as frequently mutated in

melanoma. Nat Genet 2011;43:442-446.
10. Ellis MJ, Ding L, Shen D, Luo J, Suman VJ, Wallis JW, et al. Whole-genome analysis informs breast cancer response to aromatase inhibition. Nature 2012;486:353-360.
11. Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K, Sivachenko AY, et al. The genomic complexity of primary human prostate cancer. Nature 2011;470:214-220.
12. Weinstein JN, Pommier Y. Transcriptomic analysis of the NCI-60 cancer cell lines. C R Biol 2003;326:909-920.
13. Weinstein JN. Searching for pharmacogenomic markers: the synergy between omic and hypothesis-driven research. Dis Markers 2001;17:77-88.
14. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, et al. The cancer cell line encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature 2012;483:603-607.
15. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature 2012;483:570-575.
16. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-615.
17. Yang D, Sun Y, Hu L, Zheng H, Ji P, Pecot CV, et al. Integrated analyses identify a master microRNA regulatory network for the mesenchymal subtype in serous ovarian cancer. Cancer Cell 2013;23:186-199.
18. Ciriello G, Cerami E, Sander C, Schultz N. Mutual exclusivity analysis identifies oncogenic network modules. Genome Res 2012;22:398-406.
19. Carro MS, Lim WK, Alvarez MJ, Bollo RJ, Zhao X, Snyder EY, et al. The transcriptional network for mesenchymal transformation of brain tumours. Nature 2010;463:318-325.
20. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 1997;60:496-504.
21. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001;68:700-710.
22. Rubin SC, Blackwood MA, Bandera C, Behbakht K, Benjamin I, Rebbeck TR, et al. BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: relationship to family history and implications for genetic testing. Am J Obstet Gynecol 1998;178:670-677.
23. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 2005;104:2807-2816.
24. Press JZ, De Luca A, Boyd N, Young S, Troussard A, Ridge Y, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
25. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643-646.
26. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329-1333.
27. Levine DA, Argenta PA, Yee CJ, Marshall DS, Olvera N, Bogomolniy F, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol 2003;21:4222-4227.
28. Vencken PM, Kriege M, Hoogwerf D, Beugelink S, van der Burg ME, Hooning MJ, et al. Chemosensitivity and outcome of BRCA1- and BRCA2-associated ovarian cancer patients after first-line chemotherapy compared with sporadic ovarian cancer patients. Ann Oncol 2011;22:1346-1352.
29. Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 2003;97:2187-2195.
30. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the National Israeli study of ovarian cancer. J Clin Oncol 2008;26:20-25.
31. Pal T, Permuth-Wey J, Kapoor R, Cantor A, Sutphen R. Improved survival in BRCA2 carriers with ovarian cancer. Fam Cancer 2007;6:113-119.
32. Yang D, Khan S, Sun Y, Hess K, Shmulevich I, Sood AK, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 2011;306:1557-1565.
33. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012;307:382-390.
34. Hyman DM, Zhou Q, Iasonos A, Grisham RN, Arnold AG, Phillips MF, et al. Improved survival for BRCA2-associated serous ovarian cancer compared with both BRCA-negative and BRCA1-associated serous ovarian Cancer. Cancer 2012;118:3703-3709.
35. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-921.
36. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913-917.
37. Chen A. PARP inhibitors: its role in treatment of cancer. Chin J Cancer 2011;30:463-471.
38. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M,

et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123-134.
39. Audeh MW, Carmichael J, Penson RT, Friedlander M, Powell B, Bell-McGuinn KM, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376:245-251.
40. Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512-2519.
41. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852-861.
42. Dreazen O, Klisak I, Jones G, Ho WG, Sparkes RS, Gale RP. Multiple molecular abnormalities in Ph1 chromosome positive acute lymphoblastic leukaemia. Br J Haematol 1987;67:319-324.
43. Schuster SC. Next-generation sequencing transforms today's biology. Nat Methods 2008;5:16-18.
44. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310:644-648.
45. Parker BC, Annala MJ, Cogdell DE, Granberg KJ, Sun Y, Ji P, et al. The tumorigenic FGFR3-TACC3 gene fusion escapes miR-99a regulation in glioblastoma. J Clin Invest 2013;123:855-865.
46. Warrell RP Jr, Frankel SR, Miller WH Jr, Scheinberg DA, Itri LM, Hittelman WN, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). N Engl J Med 1991;324:1385-1393.
47. Wu YM, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, et al. Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov 2013;3:636-647.
48. Singh D, Chan JM, Zoppoli P, Niola F, Sullivan R, Castano A, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. Science 2012;337:1231-1235.
49. Williams SV, Hurst CD, Knowles MA. Oncogenic FGFR3 gene fusions in bladder cancer. Hum Mol Genet 2013;22:795-803.
50. Pendergast AM, Muller AJ, Havlik MH, Maru Y, Witte ON. BCR sequences essential for transformation by the BCR-ABL oncogene bind to the ABL SH2 regulatory domain in a non-phosphotyrosine-dependent manner. Cell 1991;66:161-171.
51. Pendergast AM, Quilliam LA, Cripe LD, Bassing CH, Dai Z, Li N, et al. BCR-ABL-induced oncogenesis is mediated by direct interaction with the SH2 domain of the GRB-2 adaptor protein. Cell 1993;75:175-185.
52. Persson M, Andren Y, Mark J, Horlings HM, Persson F, Stenman G. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci U S A 2009;106: 18740-18744.
53. Esgueva R, Perner S, J LaFargue C, Scheble V, Stephan C, Lein M, et al. Prevalence of TMPRSS2-ERG and SLC45A3-ERG gene fusions in a large prostatectomy cohort. Mod Pathol 2010;23:539-546.
54. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.
55. Nahta R, Yu D, Hung MC, Hortobagyi GN, Esteva FJ. Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 2006;3:269-280.
56. Engelman JA, Jaenne PA. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. Clin Cancer Res 2008;14:2895-2899.
57. Villanueva J, Vultur A, Lee JT, Somasundaram R, Fukunaga-Kalabis M, Cipolla AK, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 2010;18:683-695.
58. Michor F, Iwasa Y, Nowak MA. Dynamics of cancer progression. Nat Rev Cancer 2004;4:197-205.
59. Govindan R, Ding L, Griffith M, Subramanian J, Dees ND, Kanchi KL, Maher CA, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-1134.
60. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 2012;481:506-510.

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