



theraprint™

decoding breast cancer.

Descriptions & References



Delivering Clinically Relevant Gene

Agendia's Research Applications

As an innovative molecular cancer diagnostics company, Agendia uses its knowledge and expertise in the application of clinically useful gene expression profiling to facilitate diagnosis, prognosis and cancer therapeutics development.

Knowledge of a tumor's gene expression can be used to predict the ability of an individual's tumor to spread and may predict a tumor's response to chemotherapy and targeted therapies. As the scientific and medical community gains a deeper understanding about the role these genes play in disease progression and treatment response, this information may offer patients access to novel therapies –and a greater level of personalized treatment.

About Agendia's TheraPrint™

Agendia's TheraPrint is a microarray-based gene expression panel of 56 genes that have been identified as potential markers for prognosis and therapeutic response to a variety of therapies. Although these genes are still in a research phase, in the future they may hold the key to a

greater level of personalized prognosis and therapy for breast cancer patients. Today, TheraPrint is offered as a research tool and for Research Use Only (R.U.O.)

The genes on TheraPrint and their potential involvement in the context of cancer therapy have been investigated in research studies and have been described in scientific publications. Some of these genes are directly targeted by existing drugs or drug types, other genes have been shown to be involved in resistance or response to therapy or to be prognostic. The results are available in the public domain.

Although there are scientific publications that discuss the involvement of these genes with regard to response or resistance to specific therapies, Agendia has not performed any studies that suggest, nor support, the use of TheraPrint results as a tool for therapeutic decision-making at the present time. Agendia, as well as other independent research centers, are actively investigating the roles these genes play in disease progression and therapeutic response with the goal of

enabling more individualized medicine. Agendia will be consistently updating its database to provide you with additional information.

Patient Selection

While this test is designed for research use only, technically any breast cancer patient may potentially benefit from the genomic information captured by this panel. By acquiring the gene expression levels of these potential targets, in advance of any adjuvant therapy, you are in essence documenting the "fingerprint" of the patient's tumor.

Decisions regarding care and treatment should not be based on a single test such as this test. More investigation is required to fully understand, and validate, how the expression levels of these genes are linked to therapeutic response.

Expression Analysis for Cancer Patients



TheraPrint Results

Using DNA microarray technology, TheraPrint measures the mRNA level of genes that are of potential interest in the context of cancer therapy. For each gene assessed, the gene expression is shown as an absolute gene expression and a relative gene expression percentile. There are no established cutoffs to determine whether a given result is high/low or active/inactive. To provide a relative indication whether a gene expression is rather low or rather high, the patient's absolute gene expression is compared to the gene expression of a reference population. The TheraPrint reference distribution was established using 373 samples from newly diagnosed untreated breast cancer patients.

The absolute gene expression result is the log₂ intensity of each gene as measured on the array ranging from 0 to 19. The value is dimensionless and cannot be directly translated to RNA concentration or copy number. The relative gene expression readout compares the expression of a given gene to expression of the same gene in the reference distribution comprised of other

breast cancer samples. The relative expression of the patient's gene is given as a percentile score. This percentile score indicates the percentage of reference samples with a lower intensity.

For example, if the absolute expression of a gene is 2 and the expression of the reference ranges from 0 to 10, then the relative gene expression percentile of this gene is 20, indicating that 20 percent of the reference samples have a lower expression, and 80% of the reference samples have a higher expression.

Agendia assumes that physicians ordering this test understand the meaning of the individual gene expression result in the context of their research.

Ordering

TheraPrint is for Research Use Only and can only be ordered in conjunction with the MammaPrint test. The panel will be performed using the same quality control measures. Your Agendia representative, or Customer Care, can provide you with the test requisition form at your request.

Agendia will perform the test on the tumor sample submitted for MammaPrint. The tissue sample should be obtained fresh, prior to formalin fixation, and placed into Agendia's FDA-cleared, room temperature RNARetain[®] molecular fixative provided within the Specimen Transportation kit. For detailed instructions on obtaining a tumor sample for testing, please refer to Agendia's Sampling Instructions provided within the Specimen Transportation kit.

Once the sample is received, Agendia will perform the analysis and provide a report of the quantitative results within 7-10 working days. Agendia performs testing at its state-of-the-art CLIA (Clinical Laboratory Improvement Act) certified and CAP (College of American Pathologists) registered and compliant genomics laboratories in Irvine, California and Amsterdam, The Netherlands.

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
BRCA1	IRIS; PSCP; BRCAI; BRCC1; RNF53; BRCA1	BRCA1/BRCA2-containing complex, subunit 1 or breast cancer 1, early onset	This gene encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability and acts as a tumor suppressor. The encoded protein combines with other tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as BASC for BRCA1-associated genome surveillance complex. This gene product associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complex. This protein thus plays a role in transcription, DNA repair of double-stranded breaks, and recombination. Mutations in this gene are responsible for approximately 40% of inherited breast cancers and more than 80% of inherited breast and ovarian cancers.	PARP inhibitors/ cisplatin
BRCA2	FAD; FADC; FAD1; BRCC2; FANCB; FANCD; FANCD1; BRCA2	Breast Cancer Type 2 susceptibility protein	Both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair. The BRCA2 protein contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase which functions in DNA repair.	PARP inhibitors/ cisplatin
C11orf30	EMSY; GL002; FLJ90741; C11orf30	chromosome 11 open reading frame 30 / EMSY protein	Regulator able to repress transcription. May play a central role in the DNA repair function of BRCA2. The EMSY gene encodes a protein that interacts with Brca2 and is amplified in some sporadic cases of human breast cancer.	PARP inhibitors/ cisplatin
FANCF	FAF; MGC126856; FANCF	Fanconi anemia, complementation group F	DNA repair protein that may operate in a postreplication repair or a cell cycle checkpoint function.	PARP inhibitors/ cisplatin
PRKCB1	PKCB; PRKCB1; PRKCB2; MGC41878; PKC-beta; PRKCB	protein kinase C, beta	Protein kinase C (PKC) is a family of serine- and threonine-specific protein kinases that can be activated by calcium and second messenger diacylglycerol. PKC family members phosphorylate a wide variety of protein targets and are known to be involved in diverse cellular signaling pathways. PKC family members also serve as major receptors for phorbol esters, a class of tumor promoters. Each member of the PKC family has a specific expression profile and is believed to play a distinct role in cells. The protein encoded by this gene is one of the PKC family members.	specific kinase inhibitors (enzastaurin hydrochloride and LY317615)
TYMS	TS; TMS; TSase; HsT422; MGC88736; TYMS	thymidylate synthetase	Thymidylate synthase catalyzes the methylation of deoxyuridylate to deoxythymidylate using 5,10-methylenetetrahydrofolate (methylene-THF) as a cofactor. This function maintains the dTMP (thymidine-5-prime monophosphate) pool critical for DNA replication and repair.	5-FU
DHFR	DHFR	dihydrofolate reductase	Dihydrofolate reductase converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the de novo synthesis of purines, thymidylic acid, and certain amino acids.	antifolate drugs
CSK	MGC117393; CSK	c-src tyrosine kinase	The Src family of kinases has nine known members, all of which are nonreceptor tyrosine kinases involved in signal transduction in both normal and cancer cells. c-Src is the best-studied member of the Src family and the one most often implicated in cancer progression. c-Src has multiple substrates that lead to diverse biologic effects, including changes in proliferation, motility, invasion, survival, and angiogenesis. Elevated Src expression has been seen in multiple solid tumors including breast cancer.	specific kinase inhibitors
VEGFA	VPF; VEGF; VEGF-A; MGC70609; VEGFA	vascular endothelial growth factor A	This gene is a member of the PDGF/VEGF growth factor family and encodes a protein that is often found as a disulfide linked homodimer. This protein is a glycosylated mitogen that specifically acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis.	Avastin
VEGFB	VRF; VEGFL; VEGFB	vascular endothelial growth factor B	Vascular endothelial growth factor (VEGF) a sub-family of growth factors, more specifically of platelet-derived growth factor family of cystine-knot growth factors. They are important signaling proteins involved in both vasculogenesis and angiogenesis.	Avastin

CLINICAL RELEVANCE	REFERENCES	COMMENTS
It has been shown that BRCA1/2 dysfunction sensitizes cell to inhibition of PARP, eventually resulting in apoptosis.	(1) Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. <i>Cell</i> . 2002 Jan 25;108(2):171-82 (2) Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. <i>Nature</i> 2005;434:917-21.	Mutation in the BRCA1 gene causes loss of function of this protein and is responsible for cancer progression and therapy response. The gene expression analysis does not indicate if this gene is mutated.
PARP inhibitors are used as targeted cancer therapy for recombination deficient cancers, such as BRCA2 tumors.	(1) Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. <i>Nature</i> 2005;434:913-7.	Mutation in the BRCA2 gene causes loss of function of this protein and is responsible for cancer progression and therapy response. The gene expression analysis does not indicate if this gene is mutated.
Amplification of the EMSY gene has been hypothesized to sensitize tumors to BRCA-directed therapies, for instance PARP inhibitors.	(1) Raouf A, Brown L, Vrcelj N, To K, Kwok W, Huntsman D, Eaves CJ. Genomic instability of human mammary epithelial cells overexpressing a truncated form of EMSY. <i>J Natl Cancer Inst</i> . 2005 Sep 7;97(17):1302-6.	A correlation between EMSY mRNA expression level and response has not yet been established.
An increasing number of studies provide evidences linking disruption of Fanconi anemia/BRCA cascade with sporadic cancers. Given that this pathway plays essential roles in response to the DNA interstrand cross-links, these cancers are expected to be chemosensitive to cross-link based therapy.	Lord CJ, Garrett MD, Ashworth A Targeting the double-strand DNA break repair pathway as a therapeutic strategy. <i>Clin Cancer Res</i> . 2006 Aug 1;12(15):4463-8.	A correlation between mRNA expression level and response has not yet been established.
There is increasing evidence that PKC-beta-selective inhibitors are effective in both preclinical and clinical trials. Enzastaurin , a potent inhibitor of PKC-beta, suppresses both tumor growth and tumor-induced angiogenesis in human tumor xenografts. Phase II trials of enzastaurin in recurrent high-grade gliomas and lymphomas have shown promising results. A similar compound, ruboxistaurin , is also under investigation in clinical trials for diabetic complications.	(1) Sledge GW Jr, Gökmen-Polar Y. Protein kinase C-beta as a therapeutic target in breast cancer. <i>Semin Oncol</i> . 2006 Jun;33(3 Suppl 9):S15-8 (2) Chen YB, LaCasce AS. Enzastaurin. : <i>Expert Opin Investig Drugs</i> . 2008 Jun;17(6):939-44.	A correlation between mRNA expression and response has not yet been established.
The enzyme has been of interest as a target for cancer chemotherapeutic agents. It is considered to be the primary site of action for 5-fluorouracil , 5-fluoro-2-prime-deoxyuridine, and some folate analogs. Thymidylate synthetase can also be inhibited by certain folate analogues, including most notably raltitrexed (trade name Tomudex) . Some studies have suggested that a correlation exists between thymidylate synthase tumor expression with pemetrexed antitumor activity.	Kuo SJ, Wang HC, Chow KC et al. Expression of rTSbeta as a 5-fluorouracil resistance marker in patients with primary breast cancer. <i>Oncol Rep</i> . 2008 Apr;19(4):881-8.	Expression of thymidylate synthase (TS) in tumor cells is frequently suggested as an important prognostic factor for patients scheduled for chemotherapy with 5-fluorouracil (5-FU). However, clinical evidence does not fully support such an anticipation.
Pemetrexed (Alimta) is a novel folate antimetabolite that primarily inhibits the enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT). It is approved for lung cancer.	(1) Martin M. Clinical experience with pemetrexed in breast cancer. <i>Semin Oncol</i> . 2006 Feb;33(1 Suppl 2):S15-8 (2) Dent SF, Gertler S, Verma S, Segal R, Young V, Goel R, Keller O, Canil C, Iscoe N. A phase II study of biweekly pemetrexed and gemcitabine in patients with metastatic breast cancer. <i>Cancer Chemother Pharmacol</i> . 2009 Jul 11. [Epub ahead of print].	A correlation between DHFR mRNA expression and response has been indicated.
Interest in these kinases has increased recently because of the development, initial clinical success, and low toxicity of pharmacologic inhibitors. Several inhibitors of the Src family kinases are in clinical development (e.g. Dasatinib); three are currently being studied in clinical trials. Initial data from these trials suggest that these agents are well tolerated.	(1) Finn RS. Targeting Src in breast cancer. <i>Ann Oncol</i> . 2008 Aug;19(8):1379-86. (2) Johnson FM, Gallick GE. SRC family nonreceptor tyrosine kinases as molecular targets for cancer therapy. <i>Anticancer Agents Med Chem</i> . 2007 (6):651-9.	A correlation between src mRNA expression and response has not been established.
Anti-VEGF therapies are important in the treatment of certain cancers and in age-related macular degeneration. They can involve monoclonal antibodies such as bevacizumab (Avastin) , antibody derivatives such as ranibizumab (Lucentis), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF: sunitinib (Sutent) , sorafenib (Nexavar) , axitinib , and pazopanib.	(1) Schneider BP, Sledge GW Jr. Drug insight: VEGF as a therapeutic target for breast cancer. <i>Nat Clin Pract Oncol</i> . 2007 Mar;4(3):181-9 (2) Hayes DF, Miller K, Sledge G. Angiogenesis as targeted breast cancer therapy. <i>Breast</i> . 2007 Dec;16 Suppl 2:S17-9.	Clinical observations have demonstrated that VEGF status is significantly correlated with neovascularization grade and prognosis in various types of solid tumors.
All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. The kinase domain is targeted by several tyrosine kinase inhibitors in development.	(1) Daniela S. Krause and Richard A. Van Etten (2005) Tyrosine Kinases as Targets for Cancer Therapy. <i>NEJM</i> Volume 353:172-187.	When VEGF is overexpressed, it can contribute to disease progression since solid cancers cannot grow beyond a limited size without an adequate blood supply. High expression of VEGF is therefore correlated with poor prognosis. If the expression is indicative for response to inhibitors is not known.

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
KRAS	NS3;KRAS1;KRAS2; RASK2;KI-RAS; C-K-RAS; K-RAS2A;K-RAS2B;K-RAS4A;K-RAS4B;	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	This gene, a Kirsten ras oncogene homolog from the mammalian ras gene family, encodes a protein that is a member of the small GTPase superfamily. Certain point mutations is responsible for an activating mutation. The transforming protein that results is implicated in various malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal carcinoma.	AZD3409 (prenylation inh.)
BRAF	BRAF1; RAFB1; B-RAF1; FLJ95109; MGC126806; MGC138284; BRAF	B-Raf Kinase	This gene encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion. Mutations in this gene have been associated with various cancers, including non-Hodgkin lymphoma, colorectal cancer, malignant melanoma, thyroid carcinoma, non-small cell lung carcinoma, and adenocarcinoma of lung.	Kinase Inhibitors (small molecules)
KDR	FLK1; CD309; VEGFR; VEGFR2; KDR	kinase insert domain receptor (a type III receptor tyrosine kinase) or soluble VEGFR2	Vascular endothelial growth factor (VEGF) is a major growth factor for endothelial cells. This gene encodes one of the two receptors of the VEGF. This receptor, known as kinase insert domain receptor, is a type III receptor tyrosine kinase. It functions as the main mediator of VEGF-induced endothelial proliferation, survival, migration, tubular morphogenesis and sprouting. The signalling and trafficking of this receptor are regulated by multiple factors, including Rab GTPase, P2Y purine nucleotide receptor, integrin alphaVbeta3, T-cell protein tyrosine phosphatase, etc..	BAY 43-9006,AG013736 (Pfizer), Bevacizumab (indirect)
ECGF1	TP; ECGF1; MNGIE; PDECGF; hPD-ECGF; TYMP	thymidine phosphorylase	This gene encodes an angiogenic factor which promotes angiogenesis in vivo and stimulates the in vitro growth of a variety of endothelial cells. It has a highly restricted target cell specificity acting only on endothelial cells. Mutations in this gene have been associated with mitochondrial neurogastrointestinal encephalomyopathy. Multiple alternatively spliced variants, encoding the same protein, have been identified.	Capecitabine (intracellular activation)
FRAP1	FRAP; MTOR; FRAP2; RAFT1; RAPT1; FLJ44809; FRAP1a	FK506 binding protein 12-rapamycin associated protein 1	FRAP1 (mTOR) is a serine/threonine kinase belonging to family of phosphatidylinositol kinase-related kinases. These mediate cellular responses to stresses such as DNA damage and nutrient deprivation. FRAP1 specifically plays a critical role in cellular growth and proliferation. Also acts as the target for the cell-cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex. Perturbations in the mTOR/PI3-kinase/AKT pathway are associated with numerous forms of cancer.	Rapamycin, CCI-779, RAD-001
MAP2K1	MEK1; MKK1; MAPKK1; PRKMK1; MAP2K1	Mitogen-activated protein kinase kinase 1	The protein encoded by this gene is a member of the dual specificity protein kinase family, which acts as a mitogen-activated protein (MAP) kinase kinase. MAP kinases, also known as extracellular signal-regulated kinases (ERKs), act as an integration point for multiple biochemical signals. This protein kinase lies upstream of MAP kinases and stimulates the enzymatic activity of MAP kinases upon wide variety of extra- and intracellular signals. As an essential component of MAP kinase signal transduction pathway, this kinase is involved in many cellular processes such as proliferation, differentiation, transcription regulation and development.	CI-1040
MAP2K2	MEK2; MKK2; MAPKK2; PRKMK2; FLJ26075; MAP2K2	Mitogen-activated protein kinase kinase 2	The protein encoded by this gene is a dual specificity protein kinase that belongs to the MAP kinase kinase family. This kinase is known to play a critical role in mitogen growth factor signal transduction. It phosphorylates and thus activates MAPK1/ERK2 and MAPK2/ERK3. The activation of this kinase itself is dependent on the Ser/Thr phosphorylation by MAP kinase kinases.	CI-1040/ Kinase inhibitors

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>K-ras is indirectly linked to response to anti-EGFR (and maybe anti VEGFR) drugs. If the protein has an activated mutation, the cell is no longer inhibited by those drugs. Additional drugs, targeted directly against K-ras are in early development. KRAS mutation is predictive of response to panitumumab and cetuximab therapy in colorectal cancer.</p>	<p>(1) Kranenburg O (2005) The KRAS oncogene: past, present, and future. <i>Biochim. Biophys. Acta</i> 1756 (2): 81–2 (2) Bos JL (1989) RAS oncogenes in human cancer: a review. <i>Cancer Res.</i> 49:4682-4689.</p>	<p>K-ras plays an important role in colon, lung, pancreas and other cancer. Activating mutations in this gene are responsible for poor response to EGFR-inhibitors.</p>
<p>Sorafenib is a small molecular inhibitor of several protein kinases. Protein kinases are overactive in many of the molecular pathways that cause cells to become cancerous. Sorafenib is unique in targeting the Raf/Mek/Erk pathway.</p>	<p>(1) Roberts PJ, Der CJ (2007) Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. <i>Oncogene</i> 26(22):3291-310 (2) King AJ et al. (2006) Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. <i>Cancer Res.</i> 66(23):11100-5.</p>	<p>BRAF inhibitors are currently used in melanoma patients with BRAF mutations. The role of BRAF gene expression in the context of breast cancer is currently under investigation.</p>
<p>Bevacizumab (Avastin), a recombinant humanised monoclonal antibody developed against VEGF, binds to soluble VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation. Pre-clinical and clinical studies have shown that bevacizumab alone or in combination with a cytotoxic agent decreases tumour growth and increases median survival time and time to tumour progression (1). Tumor-specific expression of VEGFR2 was associated with an impaired tamoxifen effect in hormone receptor-positive premenopausal breast cancer (2).</p>	<p>(1) Ranieri G, Patrino R, Ruggieri E et al. Vascular endothelial growth factor (VEGF) as a target of bevacizumab in cancer: from the biology to the clinic. <i>Curr Med Chem.</i> 2006;13(16): 1845-57 (2) Rydén L, Jirström K, Bendahl PO et al (2005) Tumor-specific expression of vascular endothelial growth factor receptor 2 but not vascular endothelial growth factor or human epidermal growth factor receptor 2 is associated with impaired response to adjuvant tamoxifen in premenopausal breast cancer. <i>J Clin Oncol</i> 23(21):4695-704.</p>	<p>Increased expression of VEGFR2 is a sign of increased vascularization.</p>
<p>Capecitabine is an orally bioavailable prodrug that is converted to 5-fluorouracil through several enzymatic steps, the last of which is mediated by thymidine phosphorylase (TP).</p>	<p>(1) Neal J, Meropol, Philip J. Gold, Robert B. Diasio et al. (2006) Thymidine Phosphorylase Expression Is Associated With Response to Capecitabine Plus Irinotecan in Patients With Metastatic Colorectal Cancer. <i>Journal of Clinical Oncology</i> 24; 4069-4077 (2) C. Andretta, C. Puppini, A. Minisini et al. (2009) Thymidine phosphorylase expression and benefit from capecitabine in patients with advanced breast cancer. <i>Ann Oncol</i>;20(2):265-71.</p>	<p>Thymidine Phosphorylase expression has been linked to response to Capecitabine (1,2). However, a cut-off level has not yet been established.</p>
<p>Dysregulation of mTOR signaling occurs in diverse human tumours, and can confer higher susceptibility to inhibitors of mTOR. Rapamycin and its derivatives, temsirolimus (CCI-779), everolimus (RAD001) and deforolimus (AP23573), specifically inhibit the function of mTOR, leading to inactivation of ribosomal S6K1 and inhibition of cap-dependent translation initiation through the 4E-BP1/eIF4E pathway. RAD001 and CCI-779 in phase I and II trials, respectively.</p>	<p>(1) Figlin RA, Brown E, Armstrong AJ (2008) NCCN Task Force Report: mTOR inhibition in solid tumors. <i>J Natl Compr Canc Netw.</i> 6 Suppl 5:S1-S20 (2) Fasolo A, Sessa C (2008). mTOR inhibitors in the treatment of cancer. <i>Expert Opin Investig Drugs.</i> 17(11):1717-34. (3) Generali D, Fox SB, Brizzi MP (2008) Down-regulation of phosphatidylinositol 3' kinase/AKT/molecular target of rapamycin metabolic pathway by primary letrozole-based therapy in human breast cancer. <i>Clin Cancer Res</i> 14(9):2673-80.</p>	<p>Expression of the pathway molecules might not significantly correlated with response or patient outcome as the extend of phosphorylation is of higher importance (3).</p>
<p>Overexpression or constitutive activation of this pathway has been shown to play an important role in the pathogenesis and progression of breast and other cancers, making the components of this signaling cascade potentially important as therapeutic targets. CI-1040, was the first MEK inhibitor to enter clinical trial. CI-1040 suffered however from poor exposure due to its poor solubility and rapid clearance, and development of compound was terminated. Optimization resulted in the discovery of the clinical candidate PD 0325901 (N-(2,3-dihydroxy-propoxy)-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide).</p>	<p>(1) Wong KK (2009) Recent developments in anti-cancer agents targeting the Ras/Raf/ MEK/ERK pathway. <i>Recent Pat Anticancer Drug Discov.</i> 4(1):28-35 (2) Friday BB, Adjei AA. (2008) Advances in targeting the Ras/Raf/MEK/Erk mitogen-activated protein kinase cascade with MEK inhibitors for cancer therapy. <i>Clin Cancer Res.</i> 14(2):342-6.</p>	<p>A correlation between mRNA expression, kinase activity and response has not yet been established.</p>
<p>see above</p>	<p>see above</p>	

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
KIT	PBT; SCFR; C-Kit; CD117; KIT	kit oncogene/ v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	This gene encodes the human homolog of the proto-oncogene c-kit. C-kit was first identified as the cellular homolog of the feline sarcoma viral oncogene v-kit. This protein is a type 3 transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor). Mutations in this gene are associated with gastrointestinal stromal tumors, mast cell disease, acute myelogenous leukemia, and piebaldism. Multiple transcript variants encoding different isoforms have been found for this gene.	Gleevec, BMS-354825 Gleevec, BMS-354825
PDGFRA	CD140A; PDGFR2; MGC74795; Rhe-PDGFR; PDGFRA	platelet-derived growth factor receptor, beta polypeptide	This gene encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin. The identity of the growth factor bound to a receptor monomer determines whether the functional receptor is a homodimer or a heterodimer, composed of both platelet-derived growth factor receptor alpha and beta polypeptides.	Gleevec, BMS-354825
PDGFRB	JTK12; PDGFR; CD140B; PDGFR1; PDGF-R-beta; PDGFRB	platelet-derived growth factor	This gene encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin. The identity of the growth factor bound to a receptor monomer determines whether the functional receptor is a homodimer or a heterodimer, composed of both platelet-derived growth factor receptor alpha and beta polypeptides. This gene is flanked on chromosome 5 by the genes for granulocyte-macrophage colony-stimulating factor and macrophage-colony stimulating factor receptor; all three genes may be implicated in the 5-q syndrome. A translocation between chromosomes 5 and 12, that fuses this gene to that of the translocation, ETV6, leukemia gene, results in chronic myeloproliferative disorder with eosinophilia.	Gleevec, BMS-354825
RAD51C	RAD51L2; MGC104277; RAD51C	RAD51 homolog C	This gene is a member of the RAD51 family of related genes, which encode strand-transfer proteins thought to be involved in recombinational repair of damaged DNA and in meiotic recombination. This gene product interacts with two other DNA repair proteins, encoded by RAD51B and XRCC3, but not with itself. This gene is one of four localized to a region of chromosome 17q23 where amplification occurs frequently in breast tumors. Overexpression of the four genes during amplification has been observed and suggests a possible role in tumor progression. Alternative splicing has been observed for this gene and two variants encoding different isoforms have been identified.	homol. Recombination (alkylators)/ DNA repair
RAD51L1	REC2; R51H2; hREC2; RAD51B; MGC34245; RAD51L1	RAD51-like 1	The protein encoded by this gene is a member of the RAD51 protein family. RAD51 family members are evolutionarily conserved proteins essential for DNA repair by homologous recombination. This protein has been shown to form a stable heterodimer with the family member RAD51C, which further interacts with the other family members, such as RAD51, XRCC2, and XRCC3. Overexpression of this gene was found to cause cell cycle G1 delay and cell apoptosis, which suggested a role of this protein in sensing DNA damage. At least three alternatively spliced transcript variants encoding distinct isoforms have been observed.	homol. Recombination (alkylators)
RAD51L3	Trad; R51H3; HsTRAD; RAD51D; RAD51L3	RAD51-like 3	The protein encoded by this gene is a member of the RAD51 protein family. RAD51 family members are highly similar to bacterial RecA and <i>Saccharomyces cerevisiae</i> Rad51, which are known to be involved in the homologous recombination and repair of DNA . This protein forms a complex with several other members of the RAD51 family, including RAD51L1, RAD51L2, and XRCC2. The protein complex formed with this protein has been shown to catalyze homologous pairing between single- and double-stranded DNA, and is thought to play a role in the early stage of recombinational repair of DNA. Several alternatively spliced transcript variants of this gene have been described.	homol. Recombination (alkylators)
XRCC2	DKFZp781P0919, RAD51-like	X-ray repair complementing defective repair in Chinese hamster cells 2	This gene encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage. This gene is involved in the repair of DNA double-strand breaks by homologous recombination and it functionally complements Chinese hamster <i>irs1</i> , a repair-deficient mutant that exhibits hypersensitivity to a number of different DNA-damaging agents.	cisplatin

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>Imatinib is a drug used to treat certain types of cancer. It is currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/Australia) as its mesylate salt, imatinib mesilate (INN). It is used in treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies. Imatinib mesylate is a tyrosine kinase receptor inhibitor targeted against PDGFR alpha and beta, c-kit and bcr-abl. These receptors regulate cellular processes such as proliferation, differentiation, and survival.</p>	<p>M. Cristofanilli P. Morandi et al. Imatinib mesylate (Gleevec®) in advanced breast cancer-expressing C-Kit or PDGFR-; clinical activity and biological correlations. Annals of Oncology 2008 19(10):1713-1719.</p>	<p>The efficacy of imatinib is determined by the mutation status of C-Kit.</p>
<p>Overexpression of growth factor receptors, including IGF, EGF, TGF-alpha, SCF and PDGF receptors, has been associated with poor prognosis in breast cancer. Therefore, a number of RTKs are already targets for novel designed drugs, which involve tyrosine kinase inhibitors and monoclonal antibodies. Imatinib (STI571), which is a selective tyrosine kinase inhibitor and particularly of c-Kit and PDGF-R, exhibited encouraging results in respect to its inhibitory effect in cell growth and invasion potential in a panel of human breast cancer cell lines (1).</p>	<p>(1) Cristofanilli M, Morandi P, Krishnamurthy S et al (2008) Imatinib mesylate (Gleevec) in advanced breast cancer-expressing C-Kit or PDGFR-beta: clinical activity and biological correlations. Ann Oncol 19(10):1713-9. (2) Roussidis AE, Theocharis AD, Tzanakakis GN. The importance of c-Kit and PDGF receptors as potential targets for molecular therapy in breast cancer. Curr Med Chem. 2007;14(7):735-43.</p>	
<p>see above</p>	<p>(1) M. Cristofanilli P. Morandi et al (2008) Imatinib mesylate (Gleevec®) in advanced breast cancer-expressing C-Kit or PDGFR-; clinical activity and biological correlations. Annals of Oncology 19(10):1713-1719 (2) Yang SX, Steinberg SM, Nguyen D et al. (2008) Gene expression profile and angiogenic marker correlates with response to neoadjuvant bevacizumab followed by bevacizumab plus chemotherapy in breast cancer. Clin Cancer Res 14(18):5893-9.</p>	<p>Expression of platelet-derived growth factor receptor-beta (PDGFR-beta) in the tumor vasculature by immunohistochemistry was significantly associated with response in neoadjuvant studies(2).</p>
<p>High-level Rad51 expression has been reported in chemoresistant or radioresistant carcinomas.</p>	<p>Ko JC, Ciou SC et al. Involvement of Rad51 in cytotoxicity induced by epidermal growth factor receptor inhibitor (gefitinib, IressaR) and chemotherapeutic agents in human lung cancer cells. Carcinogenesis. 2008 Jul;29(7):1448-58.</p>	<p>The RAD51 family of genes, including RAD51 and the five RAD51-like genes (XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3) are known to have crucial non-redundant roles in DNA repair.</p>
<p>Overexpression of Rad51 in different organisms and cell types has a wide assortment of consequences, ranging from increased homologous recombination and increased resistance to DNA damaging agents to disruption of the cell cycle and apoptotic cell death.</p>	<p>(1) Hannah L. Klein (2008) The consequences of Rad51 overexpression for normal and tumor cells. DNA Repair 7;686-693 (2) Gao K, Lockwood WW et al. Genomic analyses identify gene candidates for acquired irinotecan resistance in melanoma cells. Int J Oncol. 2008 Jun;32(6):1343-9.</p>	<p>The RAD51 family of genes, including RAD51 and the five RAD51-like genes (XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3) are known to have crucial non-redundant roles in DNA repair.</p>
<p>This protein is found to interact with BRCA1 and BRCA2, which may be important for the cellular response to DNA damage. BRCA2 is shown to regulate both the intracellular localization and DNA-binding ability of this protein. Loss of these controls following BRCA2 inactivation may be a key event leading to genomic instability and tumorigenesis.[1] Defect in homologous recombination changes the drug sensitivity profile, rendering the BRCA-deficient breast cancers sensitive to MitomycinC, cisplatin, etoposide and other drugs that produce complex double-stranded lesions in DNA.</p>	<p>(1) Daniel DC (2002). Highlight: BRCA1 and BRCA2 proteins in breast cancer. Microsc. Res. Tech. 59 (1): 68-83 (2) Pellegrini L, Yu DS, Lo T, Anand S, Lee M, Blundell TL, Venkitesan AR (2002) Insights into DNA recombination from the structure of a RAD51-BRCA2 complex. Nature 420 (6913): 287-93.</p>	<p>The RAD51 family of genes, including RAD51 and the five RAD51-like genes (XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3) are known to have crucial non-redundant roles in DNA repair.</p>
<p>Cisplatin resembles an alkylating agent. Although the exact mechanism of action is unknown, action is thought to be similar to that of the bifunctional alkylating agents, that is, possible cross-linking and interference with the function of DNA and a small effect on RNA. It is cell cycle phase-nonspecific. Stimulation of the host immune system is also possible. A naturally occurring genetic variant of human XRCC2 confers increased resistance to cisplatin-induced DNA damage.</p>	<p>(1) Powell SN, Kachnic LA.(2008) Therapeutic exploitation of tumor cell defects in homologous recombination. Anticancer Agents Med Chem 8(4):448-60. (2) Thaker J (2005) The RAD51 gene family, genetic instability and cancer. Cancer Lett 219(2):125-35.</p>	<p>The RAD51 family of genes, including RAD51 and the five RAD51-like genes (XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3) are known to have crucial non-redundant roles in DNA repair.</p>

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
XRCC3	RAD51-like	X-ray repair complementing defective repair in Chinese hamster cells 3	This gene encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage. This gene functionally complements Chinese hamster irs15F, a repair-deficient mutant that exhibits hypersensitivity to a number of different DNA-damaging agents and is chromosomally unstable. A rare microsatellite polymorphism in this gene is associated with cancer in patients of varying radiosensitivity.	5-fluorouracil,
RAF1	CRAF, RAF, c-Raf, EC2.7.11.1	v-raf-1 murine leukemia viral oncogene homolog 1	This gene is the cellular homolog of viral raf gene (v-raf). The encoded protein is a MAP kinase kinase kinase (MAP3K), which functions downstream of the Ras family of membrane associated GTPases to which it binds directly. Once activated, the cellular RAF1 protein can phosphorylate to activate the dual specificity protein kinases MEK1 and MEK2, which in turn phosphorylate to activate the serine/threonine specific protein kinases, ERK1 and ERK2. Activated ERKs are pleiotropic effectors of cell physiology and play an important role in the control of gene expression involved in the cell division cycle, apoptosis, cell differentiation and cell migration.	ISIS 5132 (antisense)
EGFR	ERBB, ERBB1, HER1, PIG61	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer.	Lapatinib (GlaxoSmithKline), cetuximab, tarveca, Iressa
FLT4	VEGFR3, PCL, EC2.7.10.1, FLT41, LMPH1A	ms-related tyrosine kinase 4	This gene encodes a tyrosine kinase receptor for vascular endothelial growth factors C and D. The protein is thought to be involved in lymphangiogenesis and maintenance of the lymphatic endothelium. Mutations in this gene cause hereditary lymphedema type IA.	anti- VEGFR
FLT3	CD135, FLK2, STK-1, STK1, OTTHUMP0000004 2340, EC2.7.10.1	fms-related tyrosine kinase 3	This gene encodes a class III receptor tyrosine kinase that regulates hematopoiesis. The receptor consists of an extracellular domain composed of five immunoglobulin-like domains, one transmembrane region, and a cytoplasmic kinase domain split into two parts by a kinase-insert domain. The receptor is activated by binding of the fms-related tyrosine kinase 3 ligand to the extracellular domain, which induces homodimer formation in the plasma membrane leading to autophosphorylation of the receptor. The activated receptor kinase subsequently phosphorylates and activates multiple cytoplasmic effector molecules in pathways involved in apoptosis, proliferation, and differentiation of hematopoietic cells in bone marrow. Mutations that result in the constitutive activation of this receptor result in acute myeloid leukemia and acute lymphoblastic leukemia.	Kinase Inhibitors (small molecules)

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>Fluorouracil is an antimetabolite of the pyrimidine analog type. Fluorouracil is considered to be cell cycle-specific for the S phase of cell division. Activity results from its conversion to an active metabolite in the tissues, and includes inhibition of DNA and RNA synthesis. XRCC3-241 C/C genotypes were associated with adverse progression-free survival. 5-fluorouracil Irinotecan and its active metabolite, SN-38, inhibit the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Irinotecan and SN-38 bind to the topoisomerase I-DNA complex and prevent religation of the DNA strand, resulting in double-strand DNA breakage and cell death. Xrcc3 overexpression in MCF-7 cell resulted in increased resistance to cisplatin/melphalan.</p>	<p>Zhiyuan Xu 1, Martin Loignon 2, Feiyu Han et al (2008) XRCC3 induces cisplatin resistance by stimulation of Rad51-related recombinational repair, S-phase check point activation, and reduced apoptosis. <i>Journal of Pharmacology And Experimental Therapeutics Fast Forward</i>. DOI: 10.1124/jpet.105.084053.</p>	<p>The RAD51 family of genes, including RAD51 and the five RAD51-like genes (XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3) are known to have crucial non-redundant roles in DNA repair.</p>
<p>Sorafenib (Nexavar, Bayer) is a small molecular inhibitor of several protein kinases. Protein kinases are overactive in many of the molecular pathways that cause cells to become cancerous. These pathways include Raf kinase, PDGF (platelet-derived growth factor), VEGF receptor 2 and 3 kinases and c Kit the receptor for Stem cell factor. A growing number of drugs target most of these pathways. Sorafenib is unique in targeting the Raf/Mek/Erk pathway.</p>	<p>(1) Wong KK (2009) Recent developments in anti-cancer agents targeting the Ras/Raf/ MEK/ERK pathway. <i>Recent Pat Anticancer Drug Discov.</i> 4(1):28-35 (2) Dal Lago L, D'Hondt V, Awada A (2008) Selected combination therapy with sorafenib: a review of clinical data and perspectives in advanced solid tumors. <i>Oncologist.</i> 2008 Aug;13(8):845-58.</p>	<p>A correlation between RAF expression and response to the kinase inhibitors is not yet established.</p>
<p>Erlotinib hydrochloride is marketed under the tradename Tarceva. Erlotinib is a highly selective TKI that is approved by the FDA and European regulators for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Gefitinib (INN) acting in a similar manner to erlotinib, trade name Iressa. Gefitinib is currently only indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have previously received chemotherapy. There is potential for its use in the treatment of other cancers where EGFR overexpression is involved. Lapatinib (INN) is an orally active chemotherapeutic drug treatment for solid tumours such as breast cancer. Pharmacologically, lapatinib is a dual tyrosine kinase inhibitor that interrupts cancer-causing cellular signals. Lapatinib inhibits the tyrosine kinase activity associated with two oncogenes, EGFR (epidermal growth factor receptor) and HER2/neu (Human EGFR type 2). Many therapeutic approaches are aimed at the EGFR. Cetuximab and panitumumab are examples of monoclonal antibody inhibitors. Other monoclonals in clinical development are zalutumumab, nimotuzumab, and matuzumab.</p>	<p>(1) Johnston JB, Navaratnam S, Pitz MW (2006) Targeting the EGFR pathway for cancer therapy. <i>Curr Med Chem</i> 13(29):3483-92 (2) Flynn JF, Wong C, Wu JM. (2009) Anti-EGFR Therapy: Mechanism and Advances in Clinical Efficacy in Breast Cancer. <i>J Oncol.</i> 2009;2009:526963.</p>	<p>Overexpression and specific mutations of EGFR have been linked to response to EGFR kinase inhibitors.</p>
<p>AZD2171 is an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and other tyrosine kinases that has shown clinical activity in NSCLC in combination with carboplatin and paclitaxel. Sunitinib (marketed as Sutent, and previously known as SU11248) is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). It inhibits receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs).</p>	<p>(1) Su JL, Yen CJ, Chen PS et al (2007) The role of the VEGF-C/VEGFR-3 axis in cancer progression. <i>Br J Cancer</i> 96(4):541-5 (2) Chow LQ, Eckhardt SG (2007). Sunitinib: from rational design to clinical efficacy. <i>J Clin Oncol.</i> 25(7):884-96.</p>	
<p>Mutations of the Flt3 receptor can lead to the development of leukemia, a cancer of bone marrow hematopoietic progenitors. Several inhibitors of the kinase are in clinical studies to investigate the role as anti-leukemic drugs (for example NVP-AST487).</p>	<p>Reilly JT (2003). "FLT3 and its role in the pathogenesis of acute myeloid leukaemia." <i>Leuk. Lymphoma</i> 44 (1): 1-7.</p>	<p>An association between mRNA expression and breast cancer has not yet been established.</p>

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
CCND1	BCL1, PRAD1, D11S287E, U21B31	cyclin D1	The protein encoded by this gene belongs to highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance throughout the cell cycle. Cyclins function as regulators of CDK kinases. This cyclin forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition. This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb. Mutations, amplification and overexpression of this gene, which alters cell cycle progression, are observed frequently in a variety of tumors and may contribute to tumorigenesis.	prognosis
CCNE1	CCNE; CCNE1	cyclin E1	The protein encoded by this gene belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance through the cell cycle. Cyclins function as regulators of CDK kinases. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event. This cyclin forms a complex with and functions as a regulatory subunit of CDK2, whose activity is required for cell cycle G1/S transition. Overexpression of this gene has been observed in many tumors, which results in chromosome instability, and thus may contribute to tumorigenesis. This protein was found to associate with, and be involved in, the phosphorylation of NPAT protein (nuclear protein mapped to the ATM locus), which participates in cell-cycle regulated histone gene expression and plays a critical role in promoting cell-cycle progression in the absence of pRB. Two alternatively spliced transcript variants of this gene, which encode distinct isoforms, have been described.	prognostic
NFKB1	KBF1; p105; EBP-1; MGC54151; NFKBp50; NFKB-p105; NF-kappa-B; DKFZp686C01211; NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	This gene encodes a 105 kD protein which can undergo cotranslational processing by the 26S proteasome to produce a 50 kD protein. The 105 kD protein is a Rel protein-specific transcription inhibitor and the 50 kD protein is a DNA binding subunit of the NF-kappaB (NF- κ B) protein complex. NF- κ B is a transcription factor that is activated by various intra- and extra-cellular stimuli such as cytokines, oxidant-free radicals, ultraviolet irradiation, and bacterial or viral products. Activated NF- κ B translocates into the nucleus and stimulates the expression of genes involved in a wide variety of biological functions; over 200 known genes are targets of NF- κ B in various cell types, under specific conditions. Inappropriate activation of NF- κ B has been associated with a number of inflammatory diseases while persistent inhibition of NF- κ B leads to inappropriate immune cell development or delayed cell growth	proteasome inhibitor bortezomib (PS341, Velcade)
NFKB2	LYT10; LYT-10; NFKB2	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 2	NFKB has been detected in numerous cell types that express cytokines, chemokines, growth factors, cell adhesion molecules, and some acute phase proteins in health and in various disease states. NFKB is activated by a wide variety of stimuli such as cytokines, oxidant-free radicals, inhaled particles, ultraviolet irradiation, and bacterial or viral products. Inappropriate activation of NF-kappa-B has been linked to inflammatory events associated with autoimmune arthritis, asthma, septic shock, lung fibrosis, glomerulonephritis, atherosclerosis, and AIDS. In contrast, complete and persistent inhibition of NF-kappa-B has been linked directly to apoptosis, inappropriate immune cell development, and delayed cell growth.	proteasome inhibitor bortezomib (PS341, Velcade)
FLT1	FLT; VEGFR1; FLT1	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)	Oncogene FLT belongs to the src gene family and is related to oncogene ROS (MIM 165020). Like other members of this family, it shows tyrosine protein kinase activity that is important for the control of cell proliferation and differentiation. Vascular endothelial growth factor (VEGF) is an important signaling protein involved in both vasculogenesis and angiogenesis. VEGF-A binds to VEGFR1. Recent work at ImClone and elsewhere has shown that VEGFR-1 expression is upregulated on tumor vasculature and on the tumor cells themselves.	anti-VEGFR1- antibodies SU-011248, AG013736 (Pfizer)
PITX2	RS; RGS; ARP1; Brx1; IDG2; IGDS; IHG2; PTX2; RIEG; IGDS2; IRID2; Otlx2; RIEG1; MGC20144; MGC111022; PITX2	paired-like homeodomain transcription factor 2	This gene encodes a member of the RIEG/PITX homeobox family, which is in the bicoid class of homeodomain proteins. The encoded protein acts as a transcription factor and regulates procollagen lysyl hydroxylase gene expression. This protein plays a role in the terminal differentiation of somatotroph and lactotroph cell phenotypes, is involved in the development of the eye, tooth and abdominal organs, and acts as a transcriptional regulator involved in basal and hormone-regulated activity of prolactin. Alternatively spliced transcript variants encoding distinct isoforms have been described.	Tamoxifen (prediction)

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>Overexpression has shwon to be prognostic and Cyclin D1 overexpression has been suggested as a negative predictive factor for tamoxifen response in postmenopausal breast cancer patients.</p>	<p>(1) Stendahl et al (2004)Cyclin D1 overexpression is a negative predictive factor for tamoxifen response in postmenopausal breast cancer patients. <i>British Journal of Cancer</i> 90,1942–1948. (2) Rudas M et al. (2008) Cyclin D1 Expression in Breast Cancer Patients Receiving Adjuvant Tamoxifen-Based Therapy. <i>Clin Cancer Res</i> 14,1767 - 1774.</p>	<p>Overexpression of Cyclin D1 has been implicated a poor prognostic factor in women with early-stage, ER – positive breast cancer who received adjuvant tamoxifen-based therapy.</p>
<p>CCNE1is an independent prognostic markers for lymph node-negative breast cancer patients, and may provide additional information for specific subgroups of patients.</p>	<p>(1)Möröy T et al (2004) Cyuclin E1. <i>Int J Biochem Cell Biol.</i> 36(8):1424-39 (2) Siewerts et al,(2006) Which cyclin E prevails as prognostic marker for breast cancer? Results from a retrospective study involving 635 lymph node-negative breast cancer patients. <i>Clin Cancer Res</i> 12(11 Pt 1):3319-28.</p>	<p>High levels of cyclin E have been associated with a short distant metastasis-free survival.</p>
<p>Bortezomib and trastuzumab prevent nuclear factor-kappaB (NF-kappaB) activation and induce nuclear accumulation of the cyclin-dependent kinase inhibitor p27(kip1), suggesting that combining bortezomib with trastuzumab could increase trastuzumab efficacy. In addition, the NF-kappaB pathway appears to play a major role in Inflammatory Breast cancer, possibly contributing to the unusual phenotype and aggressiveness of this form of breast cancer.</p>	<p>(1) Lerebours F ET AL (2008) NF-kappa B genes have a major role in inflammatory breast cancer. <i>BMC Cancer</i> 8:41.(2) Cardoso et al (2006) Bortezomib (PS-341, Velcade) increases the efficacy of trastuzumab (Herceptin) in HER-2-positive breast cancer cells in a synergistic manner. <i>Mol Cancer Ther</i> 5(12):3042-51</p>	<p>NF kappa B expression is associated with a resistant phenotype and poor prognosis.The expression is activated in response to chemotherapy and radiation.</p>
<p>Suppression of constitutive NF-kappaB activation inhibits the oncogenic potential of transformed cells and thus makes NF-kappaB an interesting new therapeutic target in cancer. Inhibition of NF-kappaB has been found to be an important mechanism of action of steroids, nonsteroidal anti-inflammatory drugs, and natural and synthetic compounds that show therapeutic and preventive activity. Newer agents targeting the proteasome, inhibitor-kappaB kinase, and other upstream kinases involved in NF-kappaB activation have shown anticancer activity in clinical or preclinical studies.</p>	<p>Reviews: (1) Sarkar FH, Li Y (2008) NF-kappaB: a potential target for cancer chemoprevention and therapy. <i>Front Biosci.</i> 13:2950-9 (2) Sharma HW (1996) The NF-kappaB transcription factor in oncogenesis. <i>Anticancer Res.</i>16(2):589-96.</p>	
<p>Vandetanib (ZD6474) is a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases and currently investigated in clinical studies. Based on preclinical validation studies,the anti-VEGFR-1 antibody IMC-18F1 also showed potential to provide clinical benefit to cancer patients. The VEGF-receptor is also indeirectly involved in response to the anti-VEGF antibodies that are currently in clinical use (e.g Avastin).</p>	<p>(1) Ghosh S et al (2008) High levels of vascular endothelial growth factor and its receptors (VEGFR-1, VEGFR-2, neuropilin-1) are associated with worse outcome in breast cancer. <i>Hum Pathol.</i> 39(12):1835-43. (2) Yan Wu et al. (2006) Anti-Vascular Endothelial Growth Factor Receptor-1 Antagonist Antibody as a Therapeutic Agent for Cancer ,<i>Clinical Cancer Research</i> 12, 6573-6584.</p>	<p>VEGFR-1 expression may be an independent poor prognosticator in patients with invasive breast carcinoma.</p>
<p>DNA methylation of the paired-like homeodomain transcription factor 2 (PITX2) gene was shown to be strongly correlated with increased risk of recurrence in node-negative, hormone receptor-positive, tamoxifen-treated breast cancer patients. Hypermethylation of PITX2 is, in cell lines, negatively associated with PITX2 mRNA expression and, in clinical specimens, positively associated with breast cancer disease progression.</p>	<p>(1) Harbeck N, Nimmrich I, Hartmann A et al. Multicenter study using paraffin-embedded tumor tissue testing PITX2 DNA methylation as a marker for outcome prediction in tamoxifen-treated, node-negative breast cancer patients. <i>J Clin Oncol.</i> 2008;26(31):5036-42. (2) Nimmerich I et al (2008) DNA hypermethylation of PITX2 is a marker of poor prognosis in untreated lymph node-negative hormone receptor-positive breast cancer patients. <i>Breast Cancer Res Treat.</i> 111(3):429-37.</p>	<p>Hypermethylation is correlated to poor prognosis and maybe correlated to decreased mRNA expression.</p>

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
ERBB3	HER3; LCCS2; ErbB-3; c-erbB3; erbB3-S; MDA-BF-1; MGC88033; c-erbB-3; p180-ErbB3; p45-sErbB3; p85-sErbB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3	This gene encodes a member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases. This membrane-bound protein has a neuregulin binding domain but not an active kinase domain. It therefore can bind this ligand but not convey the signal into the cell through protein phosphorylation. However, it does form heterodimers with other EGF receptor family members which do have kinase activity. Heterodimerization leads to the activation of pathways which lead to cell proliferation or differentiation. Amplification of this gene and/or overexpression of its protein have been reported in numerous cancers, including prostate, bladder, and breast tumors.	TK inhibitors/ EGFR inhibitors
AKT1	AKT; PKB; RAC; PRKBA; MGC99656; PKB-ALPHA; RAC-ALPHA; AKT1	v-akt murine thymoma viral oncogene homolog 1	The serine-threonine protein kinase encoded by the AKT1 gene is catalytically inactive in serum-starved primary and immortalized fibroblasts. AKT1 and the related AKT2 are activated by platelet-derived growth factor. The activation is rapid and specific, and it is abrogated by mutations in the pleckstrin homology domain of AKT1. It was shown that the activation occurs through phosphatidylinositol 3-kinase. Survival factors can suppress apoptosis in a transcription-independent manner by activating the serine/threonine kinase AKT1, which then phosphorylates and inactivates components of the apoptotic machinery. Multiple alternatively spliced transcript variants have been found for this gene.	Kinase Inhibitors (small molecules)
AURKA	AIK; ARK1; AURA; BTAK; STK6; STK7; STK15; AURORA2; MGC34538; AURKA	Aurora Kinase A	The protein encoded by this gene is a cell cycle-regulated kinase that appears to be involved in microtubule formation and/or stabilization at the spindle pole during chromosome segregation. The encoded protein is found at the centrosome in interphase cells and at the spindle poles in mitosis. This gene may play a role in tumor development and progression. A processed pseudogene of this gene has been found on chromosome 1, and an unprocessed pseudogene has been found on chromosome 10. Multiple transcript variants encoding the same protein have been found for this gene.	Kinase Inhibitors (small molecules)
BCL2	Bcl-2; BCL2	B-cell CLL/lymphoma 2	This gene encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes. Constitutive expression of BCL2, such as in the case of translocation of BCL2 to Ig heavy chain locus, is thought to be the cause of follicular lymphoma. Two transcript variants, produced by alternate splicing, differ in their C-terminal ends.	GC 3139; Genasense; small molecule inhibitors
CDH1	UVO; CDHE; ECAD; LCAM; Arc-1; CD324; CDH1	cadherin 1, type 1, E-cadherin (epithelial)	This gene is a classical cadherin from the cadherin superfamily. The encoded protein is a calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. Mutations in this gene are correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization. Identified transcript variants arise from mutation at consensus splice sites.	unknown
CDH3	CDHP; HJMD; PCAD; CDH3	cadherin 3, type 1, P-cadherin (placental)	This gene is a classical cadherin from the cadherin superfamily. The encoded protein is a calcium-dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. This gene is located in a six-cadherin cluster in a region on the long arm of chromosome 16 that is involved in loss of heterozygosity events in breast and prostate cancer. In addition, aberrant expression of this protein is observed in cervical adenocarcinomas.	anti-Pcadherin antibodies (early development), prognostic

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>In breast cancer, the partnership of ERBB2 and ERBB3 may be crucial for the aggressive properties of cancers with ERBB2 amplification, and may contribute to pre-existing and acquired resistance to therapy. This partnership creates opportunities for improving efficacy of ERBB-targeted pharmaceuticals, by interfering with coupling of ERBB2 to ERBB3 through dimerization inhibitors, and by use of therapeutic compounds that target AKT-dependent pathways activated through ERBB3. It has recently been shown that acquired resistance to cetuximab and Gefitinib can be linked to hyperactivity of ErbB-3. This is linked to an acquired overexpression of c-MET which phosphorylates ErbB-3, which in turn activates the Akt pathway.</p>	<p>(1) Stern DF. ERBB3/HER3 and ERBB2/HER2 duet in mammary development and breast cancer. <i>J Mammary Gland Biol Neoplasia</i>. 2008;13(2):215-23. (2) http://www.healthvalue.net/cmetherapies.html (3) Engelman J.A., Zejnullahu K. et al (2007). "MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling". <i>Science</i> 316 (5827): 1039–1043.</p>	<p>Expression of ERBB3 might be correlated to prognosis and drug response but a clear relationship between mRNA level and response has not been established.</p>
<p>Several studies have found Akt2 to be amplified or overexpressed at the mRNA level in various tumor cell lines and in a number of human malignancies such as colon, pancreatic and breast cancers. Many studies in the past 4-5 years have revealed a prognostic and/or predictive role of Akt phosphorylation in breast, prostate and non-small cell lung cancer. Elevated expression of the biomarker AKT1, often seen in sporadic cases of breast cancer, impedes the action of the BRCA1 protein, resulting in a phenotype similar to that of hereditary BRCA1 breast cancer.</p>	<p>(1)Rexer BN, Engelman JA, Arteaga CL. (2009) Overcoming resistance to tyrosine kinase inhibitors: lessons learned from cancer cells treated with EGFR antagonists. <i>Cell Cycle</i> 8(1):18-22 (2) Steelman LS, Stadelman KM, Chappell WH (2008) Akt as a therapeutic target in cancer. <i>Expert Opin Ther Targets</i> 12(9):1139-65 (3) Cicenas J. The potential role of Akt phosphorylation in human cancers. <i>Int J Biol Markers</i>. 2008 23(1):1-9 (3) Plo I, Laulier C, Gauthier L et al. (2008) AKT1 Inhibits Homologous Recombination by Inducing Cytoplasmic Retention of BRCA1 and RAD5. <i>Cancer Research</i> 68, 9404-9412.</p>	<p>Activation of Akt isoforms by phosphorylation appears to be more clinically significant than Akt2 amplification or overexpression.</p>
<p>Aurora A expression defines a population of patients with decreased survival, whereas Aurora B expression does not, suggesting that Aurora A might be the preferred drug target in breast cancer. Several Aurora-kinase inhibitors have been developed: ZM447439, Hesperadin, VX-680 and PHA-739358. The most advanced drugs are currently investigated in Phase II clinical trials.</p>	<p>(1) Nadler Y, Camp RL, Schwartz C et al (2008) Expression of Aurora A (but not Aurora B) is predictive of survival in breast cancer. <i>Clin Cancer Res</i>.14(14):4455-62 (2) Carvajal RD, Tse A, Schwartz GK (2006) Aurora kinases: new targets for cancer therapy. <i>Clin Cancer Res</i>. 12(23):6869-75.</p>	<p>Amplification of AURKA has been detected at higher frequency in tumors from BRCA1 and BRCA2 mutation carriers than in sporadic breast tumors.</p>
<p>Bcl-2 expression was associated with favorable histopathological features and predictors of positive clinical outcome. Loss of Bcl-2 expression seems to be linked to loss of hormonal regulatability, increased differentiation and deregulated proliferation. An antisense oligonucleotide drug Genasense (G3139) has been developed to target Bcl-2 (failed Phase III studies in melanoma). Abbott has recently described a novel inhibitor of Bcl-2, Bcl-xL and Bcl-w, known as ABT-737. ABT-737 is one among many so-called BH3 mimetic small molecule inhibitors (SMI) targeting Bcl-2 and Bcl-2-related proteins such as Bcl-xL and Bcl-w.</p>	<p>(1) Martínez-Arribas F, Alvarez T, Del Val G (2007) Bcl-2 expression in breast cancer: a comparative study at the mRNA and protein level. <i>Anticancer Res</i>.27(1A):219-22 (2) (2) Moreira JN, Santos A, Simões S. (2006) Bcl-2-targeted antisense therapy (Oblimersen sodium): towards clinical reality. <i>Rev Recent Clin Trials</i> 1(3):217-35.</p>	<p>Bcl-2 expression has been found to correlate with a better prognosis of breast cancer.</p>
<p>Loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. Loss of E-cadherin function or expression has been implicated in cancer progression and metastasis. E-cadherin downregulation decreases the strength of cellular adhesion within a tissue, resulting in an increase in cellular motility. This in turn may allow cancer cells to cross the basement membrane and invade surrounding tissues.</p>	<p>(1) Schmidmaier R, Baumann P (2008) ANTI-ADHESION evolves to a promising therapeutic concept in oncology. <i>Curr Med Chem</i> 15(10):978-90 (2) Cowin P, Rowlands TM, Hatsell SJ (2005) Cadherins and catenins in breast cancer. <i>Curr Opin Cell Biol</i>.17(5):499-508.</p>	<p>Loss of E-cadherin function or expression has been implicated in cancer progression and metastasis.</p>
<p>P-cadherin is frequently over-expressed in high-grade invasive breast carcinomas and has been reported to be an enhancer of migration and invasion of breast cancer cells, being correlated with tumour aggressiveness. In addition, expression of P-cadherin is well established as an indicator of poor prognosis in human breast cancer. P-Cadherin expression is a marker for basal subtype.</p>	<p>Paredes J, Correia AL, Ribeiro AS et al. P-cadherin expression in breast cancer: a review. <i>Breast Cancer Res</i>. 2007;9(5):214.</p>	<p>P-cadherin overexpression has been reported to be associated with proliferative high-grade histological tumors.</p>

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
CRYAB	CRYA2;CTPP2;HSPB5;CRYAB	crystallin, alpha B	The gene encodes for a protein of the Crystallin family. They constitute the major proteins of vertebrate eye lens and maintains the transparency and refractive index of the lens. Alpha crystallins can be induced by heat shock and are members of the small heat shock protein (sHSP also known as the HSP20) family.	unknown
CXCL12	PBSF;SDF1;SDF1A;SDF1B;TPAR1;SCYB12;SDF-1a;SDF-1b;TLSF-a;TLSF-b;CXCL12	chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	Stromal cell-derived factors 1-alpha and 1-beta are small cytokines that belong to the intercrine family, members of which activate leukocytes and are often induced by proinflammatory stimuli such as lipopolysaccharide, TNF (see MIM 191160), or IL1 (see MIM 147760). The intercrines are characterized by the presence of 4 conserved cysteines which form 2 disulfide bonds.	unknown
CXCL14	KS1;Kec;BMAC;BRAK;NJAC;MIP-2g;SCYB14;MGC10687;bolekine	chemokine (C-X-C motif) ligand 14	This gene belongs to the cytokine gene family which encode secreted proteins involved in immunoregulatory and inflammatory processes. The protein encoded by this gene is structurally related to the CXC (Cys-X-Cys) subfamily of cytokines. Members of this subfamily are characterized by two cysteines separated by a single amino acid. This cytokine displays chemotactic activity for monocytes but not for lymphocytes, dendritic cells, neutrophils or macrophages. It has been implicated that this cytokine is involved in the homeostasis of monocyte-derived macrophages rather than in inflammation.	unknown
ECGF1	TP;ECGF1;MNGIE;PDECGF;hPD-ECGF;TYMP	thymidine phosphorylase	This gene encodes an angiogenic factor which promotes angiogenesis in vivo and stimulates the in vitro growth of a variety of endothelial cells. It has a highly restricted target cell specificity acting only on endothelial cells. Mutations in this gene have been associated with mitochondrial neurogastrointestinal encephalomyopathy. Multiple alternatively spliced variants, encoding the same protein, have been identified.	Capecitabine (intracellular activation)
EGFR	ERBB, ERBB1, HER1, PIG61	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer.	Lapatinib (GlaxoSmithKline), cetuximab, tarveca, Iressa
ERBB4	HER4;MGC138404;p180erbB4;ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4	This gene is a member of the Tyr protein kinase family and the epidermal growth factor receptor subfamily. It encodes a single-pass type I membrane protein with multiple cysteine rich domains, a transmembrane domain, a tyrosine kinase domain, a phosphatidylinositol-3 kinase binding site and a PDZ domain binding motif. The protein binds to and is activated by neuregulins and other factors and induces a variety of cellular responses including mitogenesis and differentiation. Multiple proteolytic events allow for the release of a cytoplasmic fragment and an extracellular fragment. Mutations in this gene have been associated with cancer. Alternatively spliced variants which encode different protein isoforms have been described; however, not all variants have been fully characterized.	Tyrosine Kinase inhibitors
ESR2	Erb;ESRB;ESTRB;NR3A2;ER-BETA;ESR-BETA;ESR2	estrogen receptor 2	This gene encodes a member of the family of estrogen receptors and superfamily of nuclear receptor transcription factors. The gene product contains an N-terminal DNA binding domain and C-terminal ligand binding domain and is localized to the nucleus, cytoplasm, and mitochondria. Upon binding to 17beta-estradiol or related ligands, the encoded protein forms homo- or hetero-dimers that interact with specific DNA sequences to activate transcription. Some isoforms dominantly inhibit the activity of other estrogen receptor family members. Several alternatively spliced transcript variants of this gene have been described, but the full-length nature of some of these variants has not been fully characterized.	hormonal therapies
GSDML	GSDML;PP4052;PRO2521;GSDMB	gasdermin B	This gene encodes a member of the gasdermin-domain containing protein family. Other gasdermin-family genes are implicated in the regulation of apoptosis in epithelial cells, and are linked to cancer. Multiple transcript variants encoding different isoforms have been found for this gene.	unknown

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>These proteins have anti-apoptotic properties and are tumorigenic when expressed in cancer cells. Might be biomarkers in Head&Neck and Breast cancer.</p>	<p>Arrigo AP, Simon S, Gibert B et al. Hsp27 (HspB1) and alphaB-crystallin (HspB5) as therapeutic targets. FEBS Lett. 2007 Jul 31;581(19):3665-74.</p>	<p>There are no data available about the correlation of CRYAB mRNA expression and breast cancer.</p>
<p>The chemokine CXCL12 (SDF-1) and its cognate receptor CXCR4 were first identified in the context of trafficking and homeostasis of immune cells, such as T lymphocytes. Subsequently, it has been determined that CXCR4 regulates several key processes in a wide variety of cancers. DNA hypermethylation of CXCL12 plays an important role in the down-regulation of CXCL12 expression in breast carcinomas. Cancer cells lacking expression of CXCL12, but maintaining over-expression of CXCR4, can selectively spread to target organs in which the ligand is highly secreted (2). Data suggest that an elevated migratory signaling response to ectopic CXCL12 contributes to the metastatic potential of CXCR4-expressing mammary carcinoma cells, subsequent to epigenetic silencing of autocrine CXCL12 (3).</p>	<p>(1) Luker KE, Luker GD. Functions of CXCL12 and CXCR4 in breast cancer. Cancer Lett. 2006 Jul 8;238(1):30-41. (2) Zhou W, Jiang Z, Liu N et al. Down-regulation of CXCL12 mRNA expression by promoter hypermethylation and its association with metastatic progression in human breast carcinomas. J Cancer Res Clin Oncol. 2009 Jan;135(1):91-102 (3) Wendt MK, Cooper AN, Dwinell MB. Epigenetic silencing of CXCL12 increases the metastatic potential of mammary carcinoma cells. Oncogene. 2008 Feb 28;27(10):1461-71.</p>	<p>Overexpression of CXCL12 in tumor cells might decrease metastasis potential.</p>
<p>In breast cancer, the expression of CXCL14 was not associated with any tumor or patient characteristics analyzed (1). In head and neck squamous cell carcinoma (HNSCC) cells the expression of the chemokine BRAK/CXCL14 in head and neck squamous cell carcinoma (HNSCC) cells was down-regulated by EGF treatment, and forced expression of BRAK in tumor cells decreased the tumorigenicity of the cells in xenografts.</p>	<p>Kleer CG, Bloushtain-Qimron N, Chen YH et al. Epithelial and stromal cathepsin K and CXCL14 expression in breast tumor progression. Clin Cancer Res. 2008 Sep 1;14(17):5357-67.</p>	<p>There are no data available about the correlation of CXCL14 mRNA expression and breast cancer.</p>
<p>Capecitabine is an orally bioavailable prodrug that is converted to 5-fluorouracil through several enzymatic steps, the last of which is mediated by thymidine phosphorylase (TP).</p>	<p>(1) Neal J, Meropol, Philip J. Gold, Robert B. Diasio et al. (2006) Thymidine Phosphorylase Expression Is Associated With Response to Capecitabine Plus Irinotecan in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology 24;4069-4077 (2) C. Andretta, C. Puppini, A. Minisini et al. (2009) Thymidine phosphorylase expression and benefit from capecitabine in patients with advanced breast cancer. Ann Oncol;20(2):265-71.</p>	<p>Thymidine Phosphorylase expression has been linked to response to Capecitabine (1,2). However, a cut-off level has not yet been established.</p>
<p>Erlotinib hydrochloride is marketed under the tradename Tarceva. Erlotinib is a highly selective TKI that is approved by the FDA and European regulators for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Gefitinib (INN) acting in a similar manner to erlotinib, trade name Iressa. Gefitinib is currently only indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have previously received chemotherapy. There is potential for its use in the treatment of other cancers where EGFR overexpression is involved. Lapatinib (INN) is an orally active chemotherapeutic drug treatment for solid tumours such as breast cancer. Pharmacologically, lapatinib is a dual tyrosine kinase inhibitor that interrupts cancer-causing cellular signals. Lapatinib inhibits the tyrosine kinase activity associated with two oncogenes, EGFR (epidermal growth factor receptor) and HER2/neu (Human EGFR type 2). Many therapeutic approaches are aimed at the EGFR. Cetuximab and panitumumab are examples of monoclonal antibody inhibitors. Other monoclonals in clinical development are zalutumumab, nimotuzumab, and matuzumab.</p>	<p>(1) Johnston JB, Navaratnam S, Pitz MW (2006) Targeting the EGFR pathway for cancer therapy. Curr Med Chem 13(29):3483-92 (2) Flynn JF, Wong C, Wu JM. (2009) Anti-EGFR Therapy: Mechanism and Advances in Clinical Efficacy in Breast Cancer. J Oncol. 2009;2009:526963.</p>	<p>Overexpression and specific mutations of EGFR have been linked to response to EGFR kinase inhibitors.</p>
<p>Although expression of the ErbB4 receptor tyrosine kinase in breast cancer is generally regarded as a marker for favorable patient prognosis, controversial exceptions have been reported. A few Pan-Her inhibitors are currently in early clinical development eg. BMS-599626 and CI-1033 (Canertinib).</p>	<p>(1) Campos SM. (2008) Anti-epidermal growth factor receptor strategies for advanced breast cancer. Cancer Invest. 2008 Oct;26(8):757-68. (2) Chuu CP, Chen RY, Barkinge JL (2008) Systems-level analysis of ErbB4 signaling in breast cancer: a laboratory to clinical perspective. Mol Cancer Res.6(6):885-91.</p>	<p>High mRNA expression of ERBB4 in breast cancer might be a favorable prognostic marker.</p>
<p>ERbeta (ESR2) is an important factor in breast cancer development and therapy. Estrogen mediates its actions almost entirely by binding to estrogen receptors (ER), alpha and beta which further function as transcription factors. Selective estrogen receptor modulators (SERMs) are synthetic molecules which bind to ER and can modulate its transcriptional capabilities in different ways in diverse estrogen target tissues. Tamoxifen, the prototypical SERM, is extensively used for targeted therapy of ER positive breast cancers. Expression of ERbeta together with ERalpha favors positive responses to endocrine therapy in most studies.</p>	<p>(1) Peng J, Sengupta S, Jordan VC. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. Anticancer Agents Med Chem. 2009 9(5):481-99. (2) Fox EM, Davis RJ, Shupnik MA. ERbeta in breast cancer—onlooker, passive player, or active protector? Steroids. 2008 73(11):1039-51.</p>	<p>ESR1 (ERalpha) expression is directly correlated with prognosis and response to endocrine treatment. The ER alpha expression is provided as our part of our TargetPrint -ER, PR read-out service.</p>
<p>unknown</p>	<p>(1) Carl-McGrath S, Schneider-Stock R, Ebert M, Röcken C. Differential expression and localisation of gasdermin-like (GSDML), a novel member of the cancer-associated GSDMDC protein family, in neoplastic and non-neoplastic gastric, hepatic, and colon tissues. Pathology. 2008 Jan;40(1):13-24.</p>	<p>Correlation between gasdermin expression and breast cancer progression is under investigation.</p>

GENE	ALIAS	FULL NAME	GENE DESCRIPTION (AS DESCRIBED AT ENTREZ GENE NCBI WEB PAGE)	DRUGTYPE
IGF1R	CD221;IGFIR; JTK13; MGC18216; MGC142170; MGC142172;IGF1R	insulin-like growth factor 1 receptor	This receptor binds insulin-like growth factor with a high affinity. It has tyrosine kinase activity. The insulin-like growth factor I receptor plays a critical role in transformation events. Cleavage of the precursor generates alpha and beta subunits. It is highly overexpressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival.	anti-IGFR antibodies and IGFR-kinase inhibitors
IGF2R	MPR1; MPRI; CD222; CIMPR; M6P-R; IGF2R	insulin-like growth factor 2 receptor	The protein encoded by this gene is a receptor for both, insulin-like growth factor 2 (IGF2) and mannose 6-phosphate (M6P). The IGF2 and M6P binding sites are located on different segments of the receptor. This receptor functions in the intracellular trafficking of lysosomal enzymes, the activation of transforming growth factor beta, and the degradation of IGF2.	anti-IGFR antibodies and IGFR-kinase inhibitors
KRAS	NS3; KRAS1; KRAS2; RASK2; KI-RAS; C-K-RAS; K-RAS2A; K-RAS2B; K-RAS4A; K-RAS4B;	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	This gene, a Kirsten ras oncogene homolog from the mammalian ras gene family, encodes a protein that is a member of the small GTPase superfamily. Certain point mutations is responsible for an activating mutation. The transforming protein that results is implicated in various malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal carcinoma.	AZD3409 (prenylation inh.)
KRT17	PC; K17; PC2; PCHC1; KRT17	keratin 17	This gene encodes the type I intermediate filament chain keratin 17, expressed in nail bed, hair follicle, sebaceous glands, and other epidermal appendages. Mutations in this gene lead to Jackson-Lawler type pachyonychia congenita and steatocystoma multiplex.	marker for basal-like subtype
KRT5	K5; CK5; DDD; EBS2; KRT5A; KRT5	keratin 5	The protein encoded by this gene is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains coexpressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in the basal layer of the epidermis with family member KRT14.	marker for basal-like subtype
KRT8	K8; KO; CK8; CYK8; K2C8; CARD2; KRT8	keratin 8	This gene is a member of the type II keratin family clustered on the long arm of chromosome 12. Type I and type II keratins heteropolymerize to form intermediate-sized filaments in the cytoplasm of epithelial cells. The product of this gene typically dimerizes with keratin 18 to form an intermediate filament in simple single-layered epithelial cells. This protein plays a role in maintaining cellular structural integrity and also functions in signal transduction and cellular differentiation.	marker for luminal-like subtype
PIK3CA	PI3K; MGC142161; MGC142163; p110-alpha	phosphoinositide-3-kinase, catalytic, alpha polypeptide	Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. This gene has been found to be oncogenic.	EGFR/ Her2 and PI3K/ AKT/ mTOR inhibitors
PIK3R1	p85; GRB1; p85-ALPHA; PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	Phosphatidylinositol 3-kinase phosphorylates the inositol ring of phosphatidylinositol at the 3-prime position. The enzyme comprises a 110 kD catalytic subunit and a regulatory subunit of either 85, 55, or 50 kD. This gene encodes the 85 kD regulatory subunit.	PI3K-pathway inhibitors
PTH1H	HHM; PLP; PTHR; PTHRP; MGC14611; PTHLH	parathyroid hormone-like hormone (also: osteostatin)	The protein encoded by this gene is a member of the parathyroid hormone family. This hormone regulates endochondral bone development and epithelial-mesenchymal interactions during the formation of the mammary glands and teeth. This hormone is involved in lactation possibly by regulating the mobilization and transfer of calcium to the milk. The receptor of this hormone, PTHR1, is responsible for most cases of humoral hypercalcemia of malignancy. Four alternatively spliced transcript variants encoding two distinct isoforms have been observed.	bisphosphonates
TRIM29	ATDC; FLJ36085; TRIM29	tripartite motif-containing 29	The protein encoded by this gene belongs to the TRIM protein family. It has multiple zinc finger motifs and a leucine zipper motif. It has been proposed to form homo- or heterodimers which are involved in nucleic acid binding. Thus, it may act as a transcriptional regulatory factor involved in carcinogenesis and/or differentiation. It may also function in the suppression of radiosensitivity since it is associated with ataxia telangiectasia phenotype.	unknown

CLINICAL RELEVANCE	REFERENCES	COMMENTS
<p>Signaling through IGFR-1 in normal cells leads to the activation of multiple intracellular pathways, mediated by the receptor-associated tyrosine kinase domain, by PI-3 kinase, and by serine/threonine kinase (Akt), yielding growth and enhanced survival. In cancer cells, IGFR-1 plays an even more critical role because it contributes to the promotion of tumor growth by inhibition of the apoptosis, transformation, metastasis, and induction of angiogenesis through the vascular endothelial growth factor (VEGF). A number of companies have active research programs going now with small molecules and monoclonal antibodies to IGF-1R in the clinic.</p>	<p>(1) Hewish M, Chau I, Cunningham D. Insulin-like growth factor 1 receptor targeted therapeutics: novel compounds and novel treatment strategies for cancer medicine. <i>Recent Pat Anticancer Drug Discov.</i> 2009 4(1):54-72 (2) Zha J, O'Brien C, Savage H, Huw LY. Molecular predictors of response to a humanized anti-insulin-like growth factor-I receptor monoclonal antibody in breast and colorectal cancer. <i>Mol Cancer Ther.</i> 2009 8(8):2110-21.</p>	<p>Levels of the IGF-1R may have predictive value for response to anti-IGFR antibodies.</p>
<p>The cation-independent mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) is involved in a variety of cellular processes which become dysregulated in cancer. Its tumor suppressor role was recognized a long time ago. However, due to its multifunctionality, it is not easy to understand the extent its role in carcinogenesis.</p>	<p>(1) Martin-Kleiner I, Gall Troselj K. Mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) in carcinogenesis. <i>Cancer Lett.</i> 2009 Jul 29 (2) Macdonald RG, Byrd JC. The insulin-like growth factor II/mannose 6-phosphate receptor: implications for IGF action in breast cancer. <i>Breast Dis.</i> 2003;17:61-72.</p>	<p>The mRNA expression level of IGF2R have not been linked to breast cancer progression yet.</p>
<p>K-ras is indirectly linked to response to anti-EGFR (and maybe anti VEGFR) drugs. If the protein has an activated mutation, the cell is no longer inhibited by those drugs. Additional drugs, targeted directly against K-ras are in early development. KRAS mutation is predictive of response to panitumumab and cetuximab therapy in colorectal cancer.</p>	<p>(1) Kranenburg O (2005) The KRAS oncogene: past, present, and future. <i>Biochim. Biophys. Acta</i> 1756 (2): 81-2 (2) Bos JL (1989) RAS oncogenes in human cancer: a review. <i>Cancer Res.</i> 49:4682-4689.</p>	<p>K-ras plays an important role in colon, lung, pancreas cancer. Only the mutated version of the gene is correlated with drug response not the level of mRNA expression.</p>
<p>CK17 is a marker for basal subtype of breast cancer.</p>	<p>(1) Rakha EA, Elsheikh SE, Aleskandarany MA et al. Triple-negative breast cancer: distinguishing between basal and nonbasal subtypes. <i>Clin Cancer Res.</i> 2009 15(7):2302-10 (2) Sasa M, Bando Y, Takahashi M. Screening for basal marker expression is necessary for decision of therapeutic strategy for triple-negative breast cancer. <i>J Surg Oncol.</i> 2008 Jan 1;97(1):30-4.</p>	<p>The expression of CK17 is a marker for the basal-like subtype.</p>
<p>CK5/ 6 are marker for the basal subtype of breast cancer.</p>	<p>Rakha EA, Ellis IO. Triple-negative/basal-like breast cancer: review. <i>Pathology.</i> 2009 Jan;41(1):40-7.</p>	<p>The expression of CK5 is a marker for the basal-like subtype.</p>
<p>The cytokeratins 8/18 (KRT 8/18) are luminal-subtype specific markers. Low expression of KRT8 has been linked to poor prognosis.</p>	<p>Steinman S, Wang J, Bourne P et al. Expression of cytokeratin markers, ER-alpha, PR, HER-2/neu, and EGFR in pure ductal carcinoma in situ (DCIS) and DCIS with co-existing invasive ductal carcinoma (IDC) of the breast. <i>Ann Clin Lab Sci.</i> 2007 Spring;37(2):127-34.</p>	<p>The expression of CK8 is a marker for the luminal-like subtype.</p>
<p>A number of pharmaceutical companies have recently been working on PI3-kinase isoform specific inhibitors including the class I PI 3-kinase; for example IC486068 and IC87114 (ICOS Corporation) or GDC-0941 (Genentech) are in Phase I clinical studies.</p>	<p>(1) Rexer BN, Ghosh R, Arteaga CL. Inhibition of PI3K and MEK: it is all about combinations and biomarkers. <i>Clin Cancer Res.</i> 2009 15(14):4518-20 (2) Gustin JP, Cosgrove DP, Park BH. The PIK3CA gene as a mutated target for cancer therapy. <i>Curr Cancer Drug Targets.</i> 2008 Dec;8(8):733-40.</p>	<p>Overactivation of the protein can cause resistance to Herceptin and other EGFR-pathway drugs.</p>
<p>PIK3R1 is an indirect target as it forms dimers with the kinase subunit PI3CA that can be targeted with kinase inhibitors.</p>	<p>(1) Zhao L, Vogt PK. Class I PI3K in oncogenic cellular transformation. <i>Oncogene.</i> 2008 Sep 18;27(41):5486-96 (2) Camero A, Blanco-Aparicio C, Renner O et al. The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. <i>Curr Cancer Drug Targets.</i> 2008 May;8(3):187-98.</p>	
<p>PTHrP is linked to bone metastasis in breast cancer and to tumor-driven bone loss (osteolysis). When a tumor secretes PTHrP, this can lead to hypercalcemia. As this is sometimes the first sign of the malignancy, hypercalcemia caused by PTHrP is considered a paraneoplastic phenomenon. Parathyroid hormone-related protein (PTHrP) is an important regulator of bone remodeling. High level of PTHrP might indicate a poor response to biphosphonates.</p>	<p>(1) Fleming NI, Trivett MK, George J et al. Parathyroid hormone-related protein protects against mammary tumor emergence and is associated with monocyte infiltration in ductal carcinoma in situ. <i>Cancer Res.</i> 2009 Sep 15;69(18):7473-9 (2) Cicek M, Oursler MJ. Breast cancer bone metastasis and current small therapeutics. <i>Cancer Metastasis Rev.</i> 2006 Dec;25(4):635-44.</p>	<p>Overproduction of parathyroid hormone-related protein (PTHrP) occurs in a high proportion of primary breast cancers and is strongly implicated in their metastatic spread to bone.</p>
<p>TRIM29 has been reported to be underexpressed in prostate and breast cancer.</p>	<p>(1) Ring BZ, Seitz RS, Beck RA et al. A novel five-antibody immunohistochemical test for subclassification of lung carcinoma. <i>Mod Pathol.</i> 2009 Aug;22(8):1032-43. (2) Wang L, Heidt DG, Lee CJ et al. Oncogenic function of ATDC in pancreatic cancer through Wnt pathway activation and beta-catenin stabilization. <i>Cancer Cell.</i> 2009 Mar 3;15(3):207-19.</p>	



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DRUG TARGET PANEL
Research Use Only

CUSTOMER

Doctor:
Account:

Address:

City, St., Zip:

SPECIMEN

Requisition #:
Collection Date:
Test Request Date:
Date Received:
Report Date:
Specimen Type:
Customer Ref.:

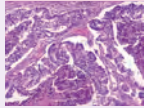
PATIENT

Patient:

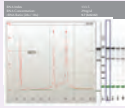
DOB:
Patient #:
Gender:
SSN:

Pathology Results

Tumor Percentage: 40%



RNA Integrity Score: 5 Excellent



Pathology Comments:

The specimen has been reviewed to determine the tumor cell percentage.

*The tumor cell percentage as reported relates to the tissue sample received by Agendia and serves as a quality control for the test. The presence of tumor cells as reported by Agendia cannot be used as a diagnosis of invasive disease.

Assay Description

Using DNA microarray technology, TheraPrint™ measures the mRNA level of genes that are of potential interest in the context of cancer therapy. Leveraging the chip capacity, the expression of each gene is assessed in multifold, assuring precise results. Provided is the absolute expression (log intensity) of the patient's genes ranging from 0 to 19.3. The relative expression percentile represents the patient's gene expression compared to a reference population of newly diagnosed untreated breast cancer patients (n=373) and indicates the percentage of reference samples with a lower intensity.

Relative Gene Expression

For each TheraPrint Gene, the absolute expression is measured and compared to the reference distribution. The relative expression of the patient's gene is given as a percentile score. This percentile score indicates the percentage of reference samples with a lower intensity. For instance, a percentile score of 91 indicates that 91% of the samples in the reference distribution had intensities lower than the intensity found in the patient's sample.

Absolute Gene Expression (log intensity)

The absolute expression level is the 2log of the intensity of each gene as measured on the Agilent microarrays (HD 8-pack). The measurement value ranges from 0 to 19.3 and is proportional to the expression level of the gene. However, the value cannot be directly translated to RNA concentration or copy number as there are no known cutoffs to determine whether a given expression level is truly high / low or activated / inactivated. The gene expression level of a given patient's results can only be compared to the gene expression level of all other samples in the reference distribution to provide relative interpretation of rather high or rather low.

Reference Distribution

The reference distribution was established using 373 samples from newly diagnosed breast cancer patients untreated with chemotherapy or hormonal therapy. Each of the samples was hybridized onto the Agilent HD 8-pack array, the log intensity of the research panel genes was measured and the results compiled. The expression distribution of the individual gene, the reference distribution is given as the 5-95% expression range on the 0 to 19.3 log intensity.

Sign Off

Cheryl Henning, M.D.

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Pathologist
Laboratory Director

References:

1. www.agendia.com/researchpanel
2. http://www.ncbi.nlm.nih.gov/sites/entrez

Regulatory Information

For In Vitro Diagnostic Use. Caution: Federal law restricts this device to sale by or on the order of a physician. Agendia, Inc. is a Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical tests that measure the mRNA expression levels of certain genes in patients diagnosed with breast cancer. Decisions regarding care on a single test such as this test. Rather, decisions on care and treatment should be based on the independent medical judgment taking into consideration all available information concerning the patient's condition, including other pathological test results, and the care in a given community.
This test was performed at Agendia's Irvine, California laboratory.

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As the scientific and medical communities gain a deeper understanding about the role these genes play in disease progression and treatment, this information may offer patients access to novel therapies – *and a greater level of personalized treatment.*



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