The CTR-Test® predicts the clinical failure of drug therapy with over 95% accuracy.[1]

CTR-Test®

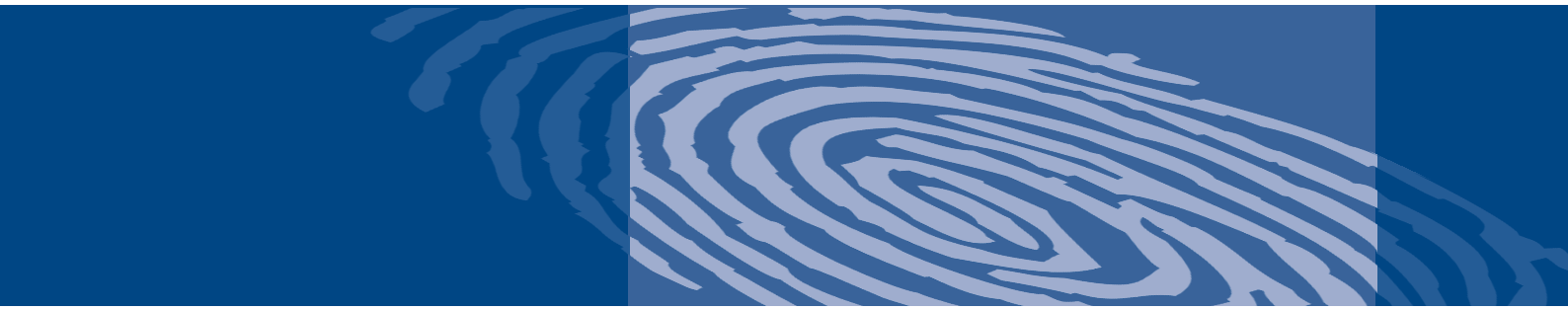
Chemotherapy-Resistance-Test

"Biochemical resistance to chemotherapy is the major impedent to successful treatment."

Vincent T. DeVita, Jr, MD

Cancer : Principle & Practice of Oncology, 4th ed.

The Step towards the Right Chemotherapy



Studies show patients receiving chemotherapy drugs that were found to be in the extreme resistance category for their tumor had significantly shorter disease-free and overall survival rates.[3, 4, 5, 14]

Therapy Select

Introduction to the CTR-Test®

Chemotherapy-Resistance-Test (CTR-Test®) is an *in vitro* diagnostic product capable of predicting resistance to chemotherapy of an individual patient with high accuracy (>95%). Chemotherapy-Resistance-Test (CTR-Test®) is a laboratory examination method, which is carried out before chemotherapy on living tumor cells, which have been removed from the patient.

Chemotherapeutic agents, that do not affect the tumor cell growth in CTR-Test®, will also not achieve an effect in patient's body with very high propability (>95%)

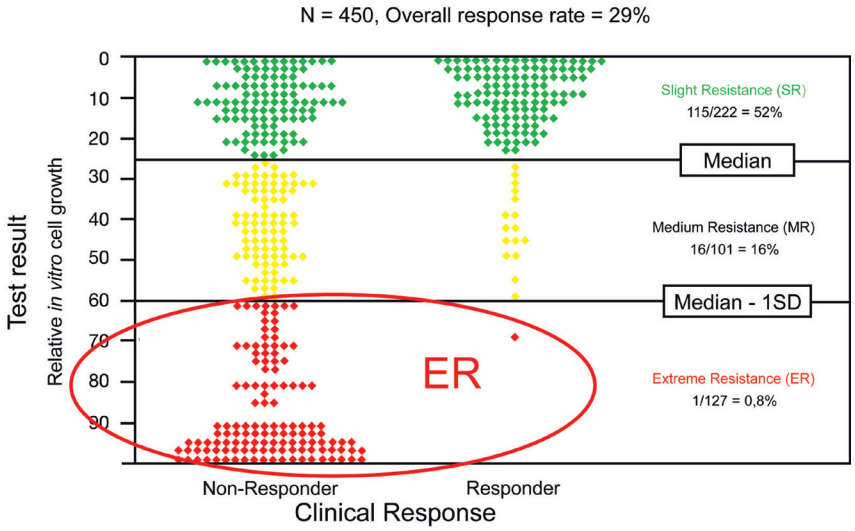
The decision in favor of a certain chemotherapeutic agent might therefore be influenced by the CTR-Test®.

By identifying ineffective substances, the test is able to spare patients unnecessary chemotherapies and the resulting side effects and cost. Valuable time for different therapies is gained and the probability that resistance to other substances (so called crossresistance) arises is reduced.

Clinical Evaluation of the CTR-Test®

Correlation of the CTR-Test® Result and Clinical Response

Kern & Weisenthal (1990)[1] showed in their publication the relation between the test result (*in vitro* resistance of a patient's tumor to a chemotherapy) and the actual clinical response of a patient to a chemotherapy. One dot in the diagram represents one patient. Overall, correlations of 450 patients are depicted.



Patients were divided up into 3 groups (y axis) according to their test result:

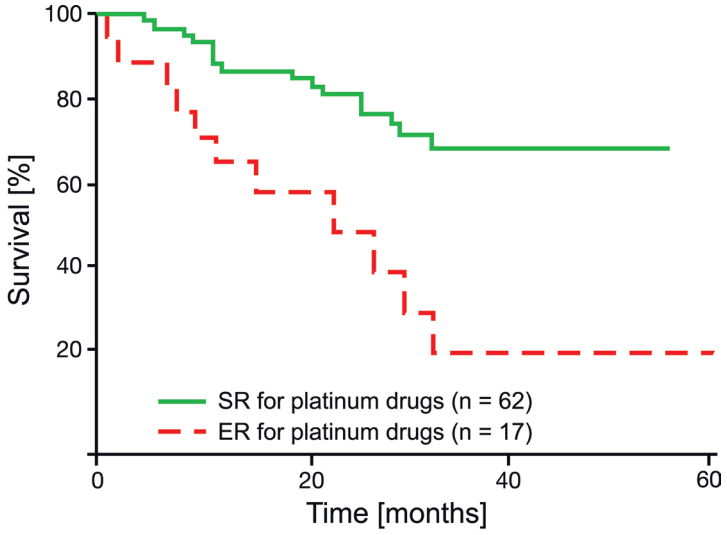
Extreme Resistance (ER): The tumor cell growth was more than one standard deviation from the median value. 126 patients (99.2%) out of 127 patients whose tumors showed an extreme level of resistance during the CTR-Test® did not respond to the chemotherapy.

Medium Resistance (MR): The tumor cell growth was higher than median growth, but smaller than one standard deviation above the median value. Tumor cells partially respond to the used agent.

Slight Resistance (SR): The tumor cell growth was below the median value. Tumor cells were only a little resistant to the used agent.

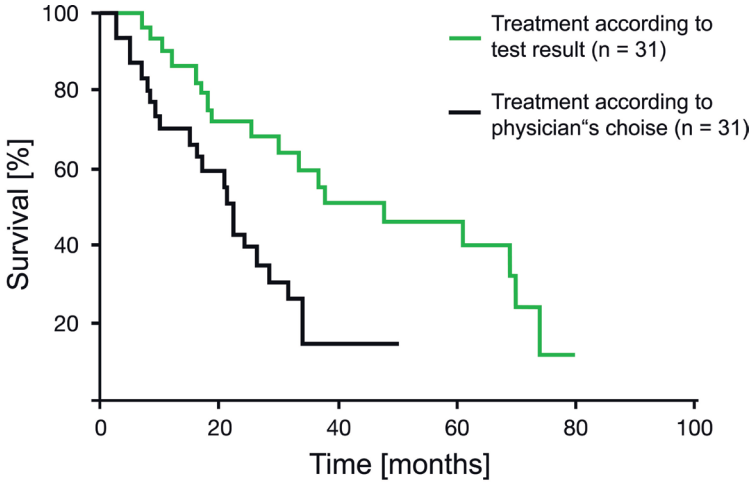
Correlation of CTR-Test® Results and Survival Time of the Patients

Holloway et al. (2002)[4] demonstrated that the time until a relapse occurred and survival times were significantly shorter for patients whose ovarian tumors displayed resistance to platinum during the CTR-Test®, if they were treated with platinum based chemotherapeutics (p=0.0003). Similar data was shown for breast cancer patients, who were administered combination chemotherapy[3].



Extending Survival Time by Choosing a Chemotherapy Based on CTR-Test® Results

Loizzi et al. (2003)[5] conducted a clinical study on platinum sensitive epithelial ovarian carcinoma. The outcome was that median survival time increased by 81% if ovarian cancer patients with recurrent tumors were treated with a therapy guided by the CTR-Test® result. Progression-free 1-year-survival rates were 90% in the group that was treated according to the test result compared to 70% in the control group (Treatment without test result) (p=0.005).



Prospective, Randomized Study on the Response of Primary Ovarian Carcinoma to a Platinum-Based Therapy

As part of the prospective, randomized, double blind EORTC study 55971 Verleye et al. (Oct. 2008)[14] investigated the response of 246 primary ovarian carcinoma patients to a platinum based therapy. They showed that in vitro resistance to platinum based therapeutics as identified by the CTR-Test® correlates well with therapy failure in clinics. Therefore extreme resistance to carboplatin was an independent significant predictive factor for failure of response to first-line platinum-based treatment in advanced ovarian cancer.

CTR-Test®-Result

The decision of selecting a certain chemotherapy for treating a tumor disease is based on a variety of aspects. The first things to take into consideration are guidelines, phase-III-study results and admission regulations for specific chemotherapeutic agents. These depend on the type and location of the tumor, degree of metastasis, number of prior treatments and staging of the patients. Preferences of the individual patient (age, condition and side effects of prior therapies) are also included in the decision.

After taking these factors into account, the CTR-Test® is able to identify unsuitable therapies because it uncovers agents to which the tumor is probably (>95%) resistant. The decision in favor of a certain chemotherapeutic agent can therefore be influenced by the CTR-Test®.

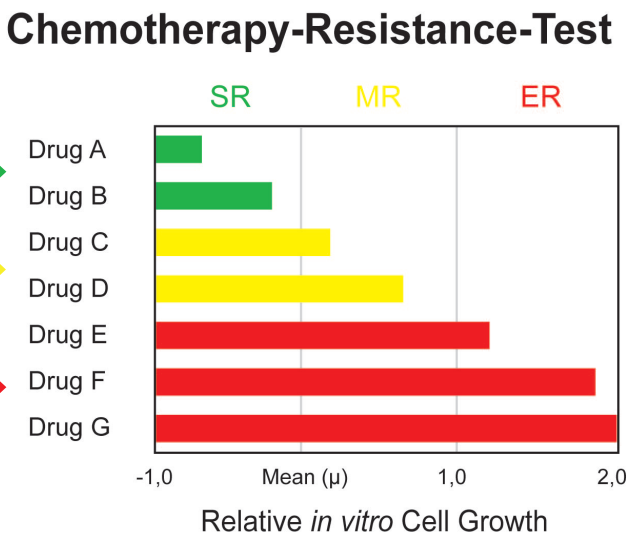
The following diagram shows an exemplary test result of a cancer patient. Seven agents were tested.

The tumor of the patient displays an **Extreme Resistance (ER)** to three chemotherapeutic agents. The physician is now able to exclude these ineffective drugs and to avoid unnecessary side effects. In this case, an alternative and effective therapy can be administered, which uses agents that were categorized as slightly resistant (SR). This increases the patient's chance to receive a successful therapy.

Slight Resistance (SR)
This means tumor cell growth was strongly inhibited by the tested chemotherapeutic agent compared to an untreated control group.
These agents are most likely to lead to an effective chemotherapy. However, the CTR-Test® was specifically developed to identify resistance. A success of the therapy is therefore not guaranteed.

Medium Resistance (MR)
This means tumor cell growth was only little inhibited by the tested chemotherapeutic agent compared to an untreated control group.
Ideally, these agents should not be used because there is an increased probability that the therapy will fail.

Extreme Resistance (ER)
This means tumor cell growth was not inhibited by the tested chemotherapeutic agent compared to an untreated control group.
These agents should not be used because a therapy failure is to be expected.



CTR-Test® Area of Application

- The CTR-Test® is in principle applicable to:
  - All types of solid tumors
    Solid tumors are those kinds of cancer which originate in different organs. The most frequently tested types of cancer are breast cancer, cervical cancer, colorectal cancer, ovarian cancer, sarcoma and skin cancer.
  - Malignant effusion including ascites and pleural effusion

- The CTR-Test® is mostly used when no clear treatment regimen can be recommended. This is the situation for the following cases:
  - Several chemotherapeutic agents are equally suitable for treating a certain type of cancer (according to guidelines).
  - Recurrent tumors, when there are no guidelines available.
  - Origin of the tumor is unknown.
  - Rare tumor types, for which no guidelines exist.

CTR-Test® Drug Selection

The treating physician can choose for patients standard drug panels according to the patients' tumor types and/or he can create his own customer specifc drug panels. There are at least 33 validated drugs available and more drugs will be added in the future. The physician has the option to get tested either up to 7 drugs (or drug combinations) or up to 14 drugs (or drug combinations).

Standard Drug Panels for the Different Tumor Types*

Lung (non-small cell, NSCLC)	Endometrial CA	Glioma	Colorectal CA
1. Cisplatin	1. Cisplatin	1. Temozolomide	1. Fluorouracil
2. Paclitaxel	2. Paclitaxel	2. Carmustine	2. Irinotecan
3. Vinorelbine	3. Doxorubicin	3. Cisplatin	3. Fluorouracil + Irinotecan
4. Etoposide	4. Ifosfamide	4. Cyclophosphamide	4. Oxaliplatin
5. Gemcitabine	5. Etoposide	5. Vincristine	5. Topotecan
6. Topotecan	6. Cyclophosphamide	6. Doxorubicin	6. Capecitabine
7. Carboplatin	7. Topotecan	7. Etoposide	7. Floxuridin
Stomach/Gastric CA (non colorectal)	**Mamma CA**	**Melanoma**	**Ovarian CA**
1. Fluorouracil	1. Fluorouracil	1. Cisplatin	1. Carboplatin
2. Mitomycin C	2. Epirubicin	2. Temozolomide	2. Paclitaxel
3. Doxorubicin	3. Cyclophosphamide	3. Vinblastine	3. Topotecan
4. Cisplatin	4. Docetaxel	4. Docetaxel	4. Doxorubicin (liposomal)
5. Etoposide	5. Paclitaxel	5. Vinorelbine	5. Etoposide
6. Gemcitabine	6. Vinorelbine	6. Gemcitabine	6. Gemcitabine
7. Paclitaxel	7. Doxorubicin	7. Vinorelbine + Docetaxel	7. Carboplatin + Paclitaxel
Pancreatic CA	**Sarcoma**	**Cervical CA**	**Unknown Origin**
1. Gemcitabine	1. Doxorubicin	1. Cisplatin	1. Cisplatin
2. Fluorouracil	2. Ifosfamide	2. Ifosfamide	2. Doxorubicin
3. Ifosfamide	3. Temozolomide	3. Vinblastine	3. Fluorouracil
4. Doxorubicin	4. Cisplatin	4. Paclitaxel	4. Cyclophosphamide
5. Irinotecan	5. Docetaxel	5. Topotecan	5. Paclitaxel
6. Mitomycin C	6. Gemcitabine	6. Doxorubicin	6. Topotecan
7. Docetaxel	7. Topotecan	7. Fluorouracil	7. Etoposide

* Standard drug panels are reviewed frequently and are subject to change.

Studies and Publications

More than 40 publications about the CTR-Test® have come out since 1990.In total, 17 clinical studies with more than 2,000 examined patients have been published. These studies prove the predictive power of the test and the benefit for the patient. On top of that, 10 validation studies with more than 20,000 patients have been conducted to verify the test on patient's specimens.

The CTR-Test® has been carried out more than 150,000 times. Therefore it is the leading technique to identify resistance to chemotherapy before administration to the patient and to spare the patient ineffective substances.

Thus, the CTR-Test® definitely is no experimental method, but an established standard procedure. The CTR-Test® is the most established method for testing resistance to chemotherapy worldwide and is exclusively offered by TherapySelect.

Clinical Studies

1. **Highly specific prediction of antineoplastic drug resistance with an in vitro assay using suprapharmacologic drug exposures.** Kern DH, Weisenthal LM. J Natl Cancer Inst. 1990 Apr 4;82(7):582-8.
2. **Cost-effective treatment of women with advanced ovarian cancer by cytoreductive surgery and chemotherapy directed by an in vitro assay for drug resistance.** Orr JW Jr, Orr P, Kern DH. Cancer J Sci Am. 1999 May-Jun;5(3):174-8.
3. **Breast cancer survival and in vitro tumor response in the extreme drug resistance assay.** Mehta RS, Bornstein R, Yu IR, Parker RJ, McLaren CE, Nguyen KP, Li KT, Fruehauf JP. Breast Cancer Res Treat. 2001 Apr;66(3):225-37.
4. **Association between in vitro platinum resistance in the EDR assay and clinical outcomes for ovarian cancer patients.** Holloway RW, Mehta RS, Finkler NJ, Li KT, McLaren CE, Parker RJ, Fruehauf JP. Gynecol Oncol. 2002 Oct;87(1):8-16.
5. **Survival outcomes in patients with recurrent ovarian cancer who were treated with chemoresistance assay-guided chemotherapy.** Loizzi V, Chan JK, Osann K, Cappuccini F, DiSaia PJ, Berman ML. Am J Obstet Gynecol. 2003 Nov;189(5):1301-7.
6. **A prospective blinded study of the predictive value of an extreme drug resistance assay in patients receiving CPT-11 for recurrent glioma.** Parker RJ, Fruehauf JP, Mehta R, Filka E, Cloughesy T. J Neurooncol. 2004 Feb;66(3):365-75.
7. **Differences of chemoresistance assay between invasive micropapillary / low-grade serous ovarian carcinoma and high-grade serous ovarian carcinoma.** Santillan A, Kim YW, Zahurak ML, Gardner GJ, Giuntoli RL, Shih IM, Bristow RE. Int J Genecol Cancer 2007. 2007 May-Jun;17(3):601-6.
8. **Extreme drug resistance is common after prior exposure to paclitaxel.** Geisler JP, Linnemeier GC, Thomas AJ, Manahan KJ. Gynecologic Oncology. 2007;106:538-540.
9. **In vitro extreme drug resistance assay to taxanes and platinum compounds for the prediction of clinical outcomes in epithelial ovarian cancer: a prospective cohort study.** Kim HS, Kim TJ, Chung HH, Kim JW, Kim BG, Park NH, Song YS, Bae DS, Kang SB. Journal of Cancer Research and Clinical Oncology. 2009 Nov;135(11):1513-20.
10. **Low drug resistance to both platinum and taxane chemotherapy on an in vitro drug resistance assay predicts improved survival in patients with advanced epithelial ovarian, fallopian, and peritoneal cancer.** Matsuo K, Bond VK, Eno ML, Im DD, Rosenshein NB. International Journal of Cancer. 2009 Dec 1;125(11):2721-7.
11. **Chemotherapy time interval and development of platinum and taxane resistance in ovarian, fallopian, and peritoneal carcinoma.** Matsuo K, Eno ML, Im DD, Rosenshein NB. Archives Gynecology and Obstetrics. 2010 Feb;281(2):325-8.
12. **Survival among patients with platinum resistant, locally advanced non-small cell lung cancer treated with platinum-based therapy.** d'Amato TA, Pettiford BL, Schuchert MJ, Parker RJ, Ricketts WA, Luketich JD, Landreneau RJ. Annals of Surgical Oncology. 2009 Oct;16(10):2848-55.
13. **Efficacy of taxane and platinum-based chemotherapy guided by extreme drug resistance assay in patients with epithelial ovarian cancer.** Joo WD, Lee JY, Kim JH, Yoo HJ, Roh HJ, Park J-Y, Kim D-Y, Kim Y-M, Kim Y-T, Nam J-H. J Gynecol Oncol. 2009 June;20(2):96-100.
14. **Extreme drug resistance for carboplatin predicts resistance to first line therapy in advanced stage ovarian cancer: results from the EORTC-GCG/NCIC-CTG neoadjuvant trial.** Verleye L, Coens C, Amant F, van der Burg MEL, Johnson N, Verheijen R, Casado A, Reed NS, Parker RJ, Vergote I. Communication at the 12th Biennial meeting International Gynecologic Cancer Society IGCS, Bangkok, Thailand, October 25-28, 2008 (abs.).

Validation Studies

1. **Heterogeneity of drug resistance in human breast and ovarian cancers.** Kern DH. Cancer J Sci Am. 1998 Jan-Feb;4(1):41-5.
2. **Factors associated with success of the extreme drug resistance assay in primary breast cancer specimens.** Ellis RJ, Fabian CJ, Kimler BF, Tawfik O, Mayo MS, Decelis CR, Jewell WR, Connor C, Modrell C, Praeger M, McGinness M, Mehta R, Fruehauf JP. Breast Cancer Res Treat. 2002 Jan;71(2):95-102.
3. **Extreme drug resistance in primary brain tumors: in vitro analysis of 64 resection specimens.** Haroun RI, Clatterbuck RE, Gibbons MC, Burger PC, Parker R, Fruehauf JP, Brem H. J Neurooncol. 2002 Jun;58(2):115-23.
4. **In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer.** Cloven NG, Kyshtoobayeva A, Burger RA, Yu IR, Fruehauf JP. Gynecol Oncol. 2004 Jan;92(1):160-6.Conservation of in vitro drug resistance patterns in epithelial ovarian carcinoma.
5. **Prevalence of in vitro extreme chemotherapy resistance in resected non-small cell lung cancer.** d'Amato TA, Landreneau RJ, McKenna RJ, Santos, RS, Parker RJ. Annals of Thoracic Surgery, 2006, 81: 440-447.

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