
GISCi
Gruppo Italiano Screening del Cervicocarcinoma
27 • 28 ottobre, Verona
CONVEGNO
NAZIONALE
GISCi 2022

La Diagnostica Molecolare di Precisione nella prevenzione dei tumori femminili. Sfide e prospettive

Giulia Borghese

Paolo Casadio

U.O. Ginecologia e Fisiopatologia della Riproduzione Umana

Prof. R. Seracchioli

IRCCS Policlinico di Sant'Orsola, Bologna

Carcinoma mammario

- Tumore maligno femminile più frequente nel mondo
- Causa principale di morte cancro-relata nelle donne
- Incidenza > in Nord America, Australia/Nuova Zelanda, Europa Occidentale e Settentrionale, < in Asia e Africa sub-sahariana

- **Italia: 55.000 nuove diagnosi** di carcinomi della mammella femminile **nel 2020**
- **2021** stimati **12.500 decessi**
- **sopravvivenza** netta a 5 anni dalla diagnosi è dell'**88%**
- **prima causa di morte per tumore nelle donne**

AIOM Associazione Italiana di Oncologia Medica

Ministero della Salute

AU Siegel RL et al., Cancer J Clin. 2021

Carcinoma cervicale

- Nel Mondo, nel 2020 604.000 nuovi casi e 342.000 decessi
- Quarto tumore per incidenza nel sesso femminile
- terzo ginecologico (dopo endometrio e ovaia) nei paesi "high-income"
- In paesi senza programmi di screening, secondo tumore più frequente nelle donne (15.7 per 100,000 donne) e terza causa di mortalità cancro-relata (8.3 per 100,000)
- Si stima che circa **l'84%** dei casi di tumore cervicale si verifichi attualmente nei Paesi in via di sviluppo

Sung H .et al., CA Cancer J Clin. 2021

Carcinoma endometriale

Il **carcinoma dell'endometrio è il più frequente tumore dell'apparato genitale** nei paesi "high-income"

Nel Mondo, nel 2020, 417.000 nuovi casi e 97.000 decessi

sesto tumore per incidenza nel sesso femminile

Incidenza in aumento!

Picco di incidenza tra I 60 e I 70 anni, ma **2-5% delle diagnosi in donne < 40 aa**

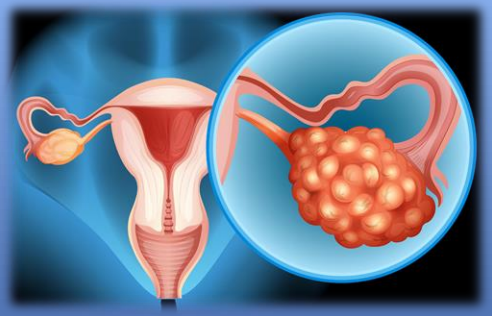
In Italia, circa 8300 nuovi casi ogni anno

tassi di incidenza variano di 10 volte tra le regioni del mondo

tassi più alti in Nord America, **Europa**, Micronesia/Polinesia e Australia/Nuova Zelanda, tassi più bassi nella maggior parte delle regioni africane e nell'Asia centro-meridionale

AU Siegel RL et al., Cancer J Clin. 2021

Carcinoma ovarico



2020: 314.000 nuove diagnosi di carcinoma ovarico

207.000 decessi

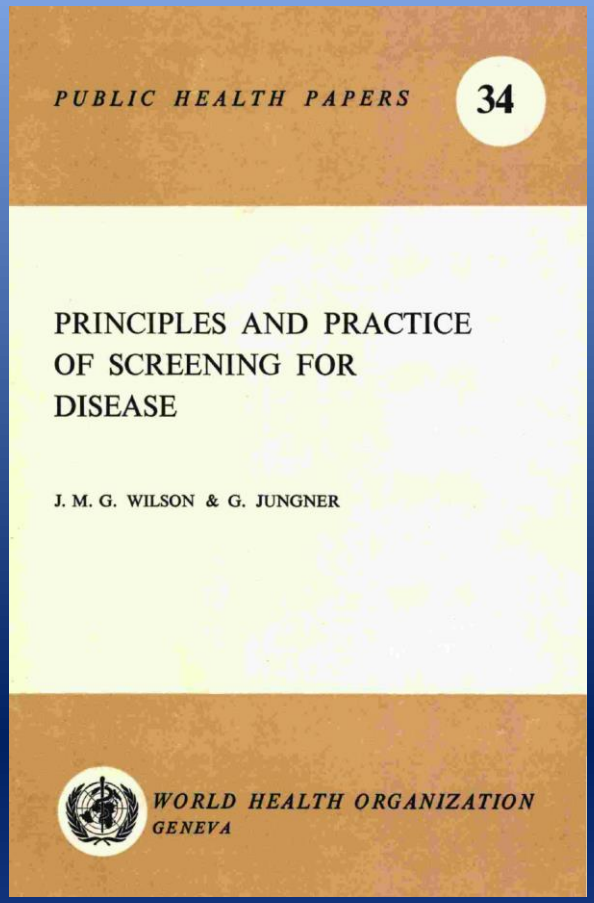
Terzo tumore del tratto genitale più comune al mondo dopo endometrio e cervice *(age standardized incidence for ovarian cancer: 6.6 per 100,000 women)*

secondo nei paesi "high income"

Associazione Italiana di Oncologia (AIOM) e Associazione Italiana dei Registri Tumori (AIRTUM) hanno calcolato che nel nostro paese vi sono stati 5.200 nuovi casi di tumore ovarico nel 2020

La possibilità di sviluppare questa neoplasia nell'arco della vita è pari a **1/82 donne**

AU Siegel RL et al., Cancer J Clin. 2021



PRINCIPLES AND PRACTICE OF SCREENING FOR DISEASE

J. M. G. WILSON
Principal Medical Officer, Ministry of Health, London, England

TABLE 2. **Wilson and Jungner Criteria for Disease Screening (Adopted by the World Health Organization)**

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognized disease
3. Facilities for diagnosis and treatment should be available
4. There should be a latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on who to treat as patients
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case finding should be a continuing process and not a "once and for all" project

From World Health Organization.[6]

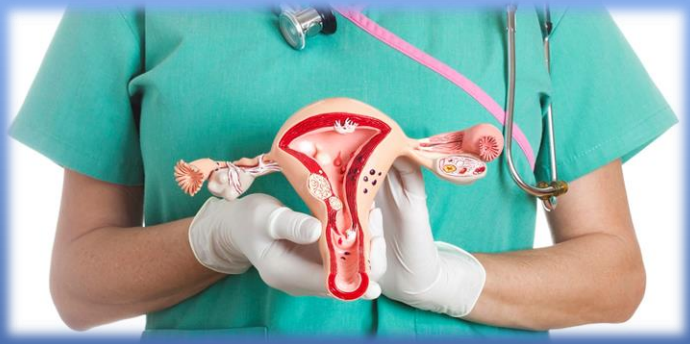
Attualmente screening disponibile per solo per cervicocarcinoma (HPV test, PAP test) e carcinoma della mammella

NON disponibili metodiche di screening per carcinoma endometriale e ovarico: tumori "orfani"!

NON accordo sui programmi di screening stessi

Leading medical groups have conflicting guidelines. The American College of Obstetricians and Gynecologists (ACOG) and the National Comprehensive Cancer Network (NCCN) say starting at 40 is best. The U.S. Preventive Services Task Force (USPSTF) says women can wait until 50. And in October, the American Cancer Society (ACS) added to the confusion by revising its guidelines. For years, the ACS recommended women start mammograms at age 40, but the ACS now recommends starting at age 45, or at 40 if the patient chooses. The groups also vary on how often mammograms should be done. ACOG says annually, USPSTF says every two years, and the most recent ACS guidelines suggest getting annual mammograms between ages 45 and 54; after that, they say every two years is OK.

Carcinoma endometriale



- NON evidenza sufficiente per programma di screening nella popolazione generale
- Non evidenza di alta qualiità a supporto dell'efficacia dello screening nella popolazione generale nel ridurre la mortalità
- Endometrio: **sot**
- Nuovi marcato
  metodiche di s

uicc
global cancer control

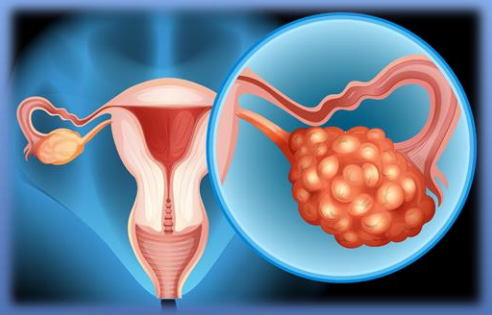
IJC
International Journal of Cancer

New perspectives on screening and early detection of endometrial cancer

Laura Costas[1], Jon Frias-Gomez[1], Magdalena Guardiola[1], Yolanda Benavente[1,2], Marta Pineda[3], Miquel Á. Pavón[1,4], José M. Martínez[5], Maite Climent[5], Marc Barahona[5], Júlia Canet[3], Sonia Paytubi[1], Mónica Salinas[3], Luis Palomero[6], Ilaria Bianchi[7], Jaume Reventós[8], Gabriel Capellà[3,4], Mireia Diaz[1,4], August Vidal[4,9], Josep M. Piulats[4,10], Álvaro Aytés[6], Jordi Ponce[5], Joan Brunet[3,4,11], Francesc X. Bosch[1,4], Xavier Matias-Guiu[4,9], Laia Alemany[1,2†] and Silvia de Sanjosé[2,12†], on behalf of the Screenwide Team

Sung H .et al., CA Cancer J Clin. 2021; Costas L. et al., Int. J. Cancer 2019

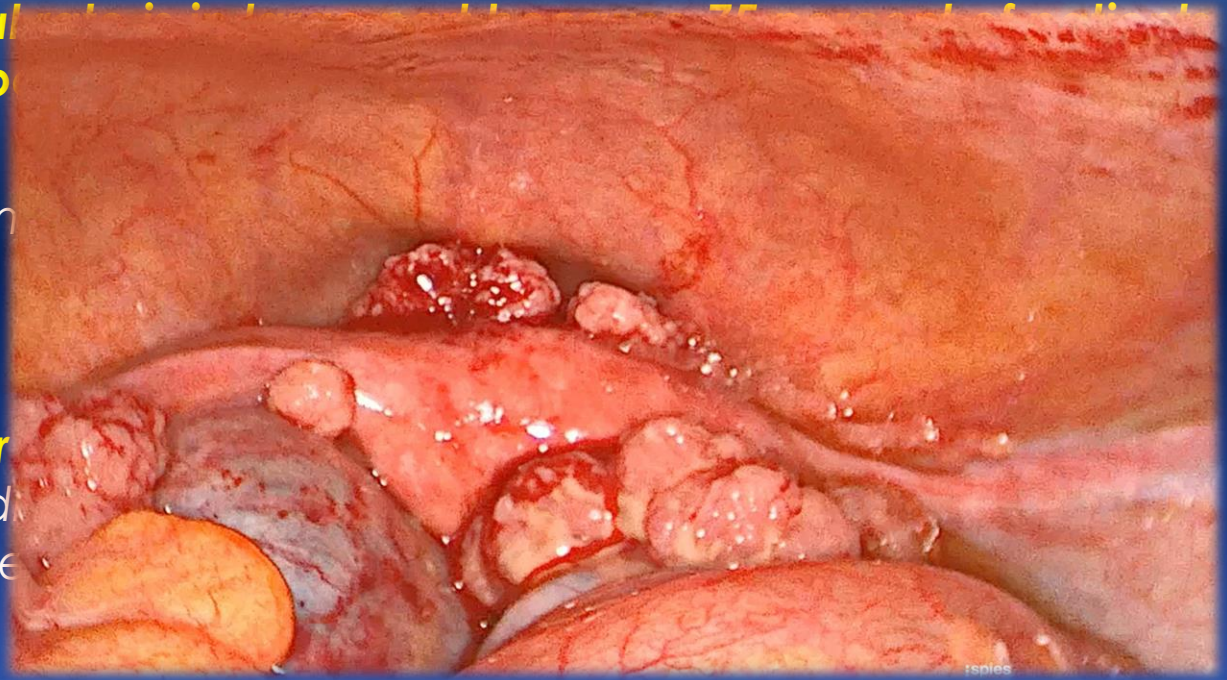
Carcinoma ovarico



Ovaio: la diagnosi ad oggi è tardiva
(sintomatica o al IV stadio)

"The poor overall survival
have spread of cancer b

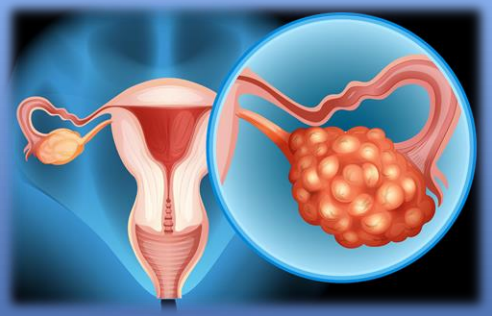
..within the entire abdom



*"**Five-year***
regional d
stage I dise

Barret J. et al., Nature Communications 2022

Carcinoma ovarico



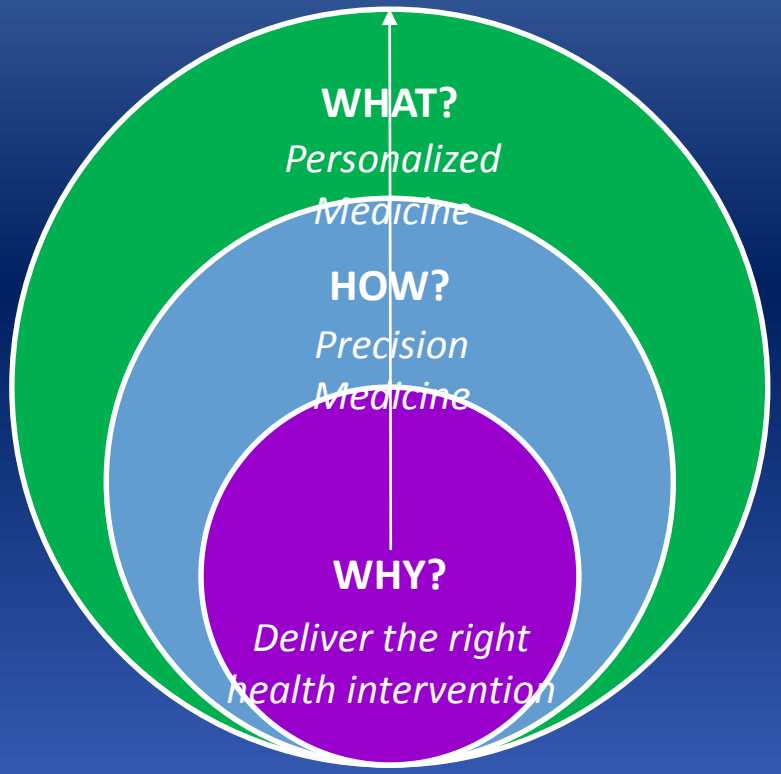
Potenziali screening: marker sierico CA125, ecografia transvaginale

NON evidenza di beneficio su sopravvivenza nella popolazione generale!

Alto tasso di falsi positivi e over-treatment

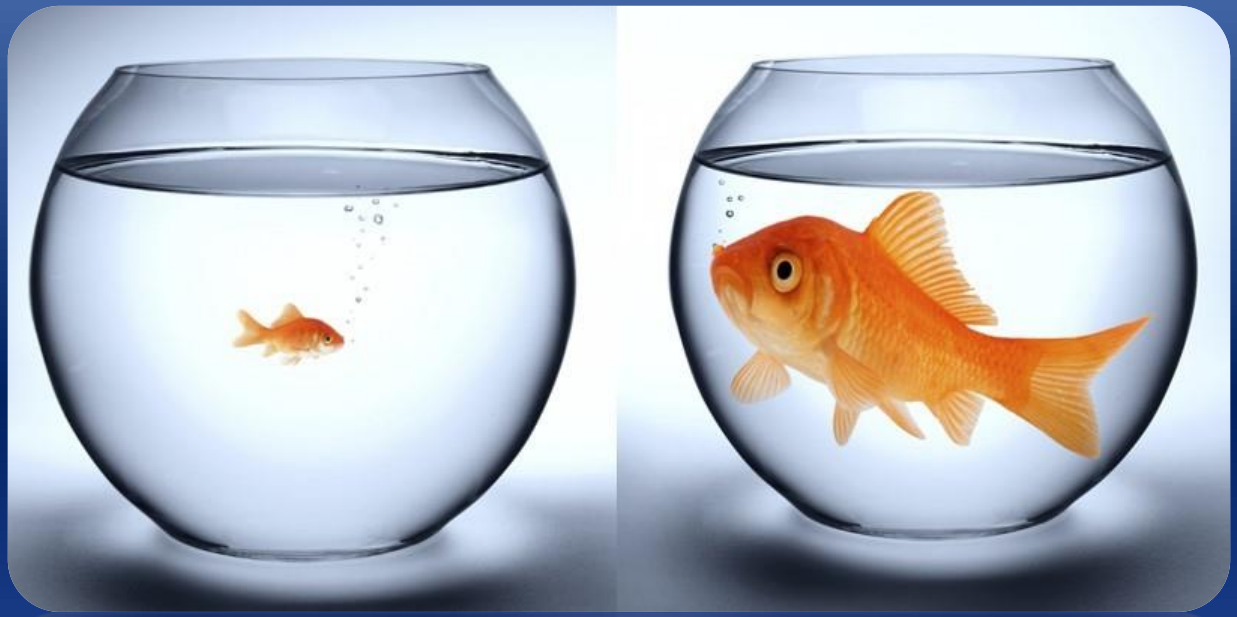
Kurman RJ et al., Am J Obstet Gynecol 2008; Barret J. et al., Nature Communications 2022

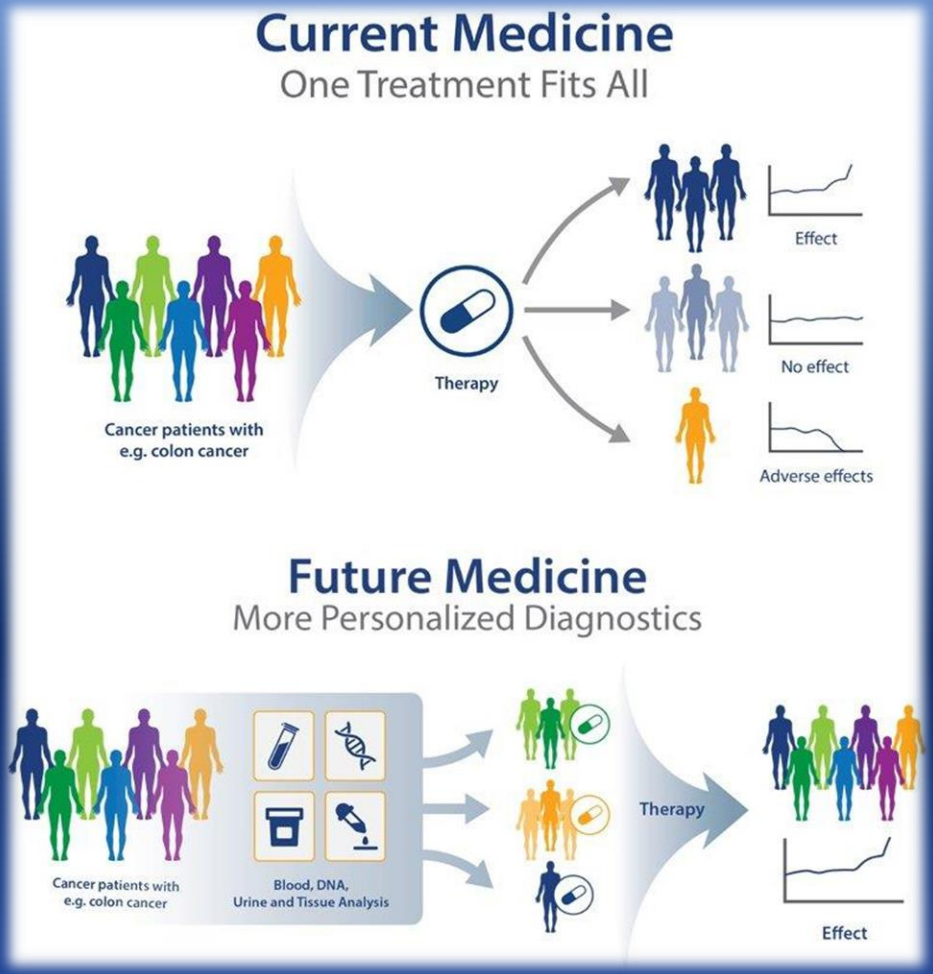
Sempre più strumenti e tecnologie, dalla **genomica** ai **big data**, possono essere utilizzati per aiutare a fornire il giusto intervento sanitario, al momento giusto, che va dal trattamento farmacologico personalizzato a scelte di sanità pubblica / di medicina di popolazione di precisione.

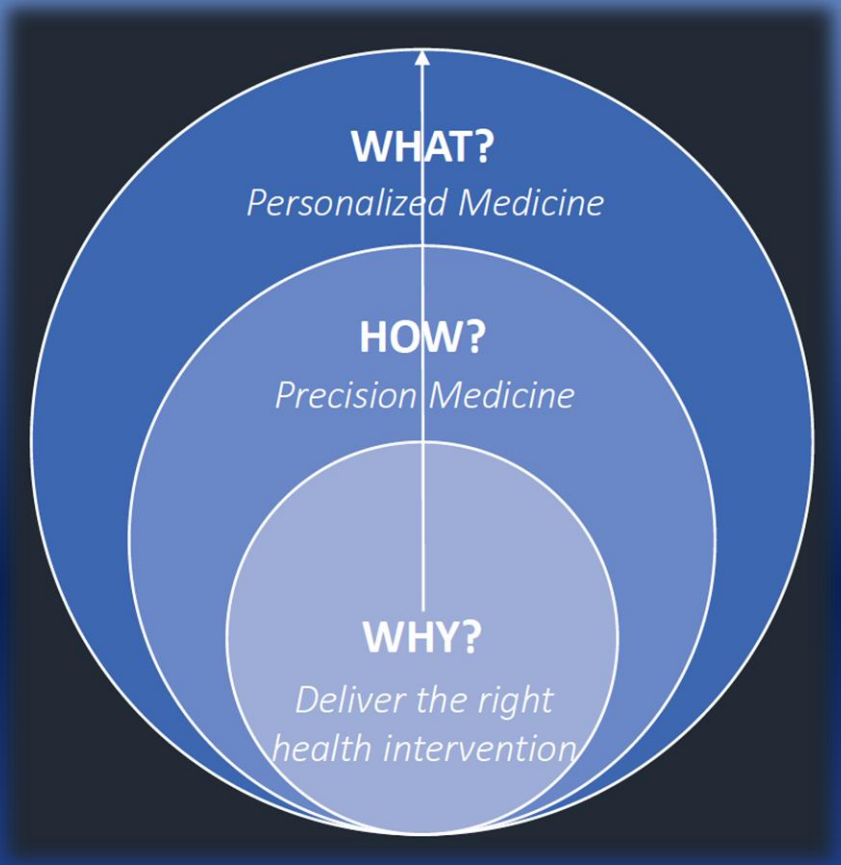


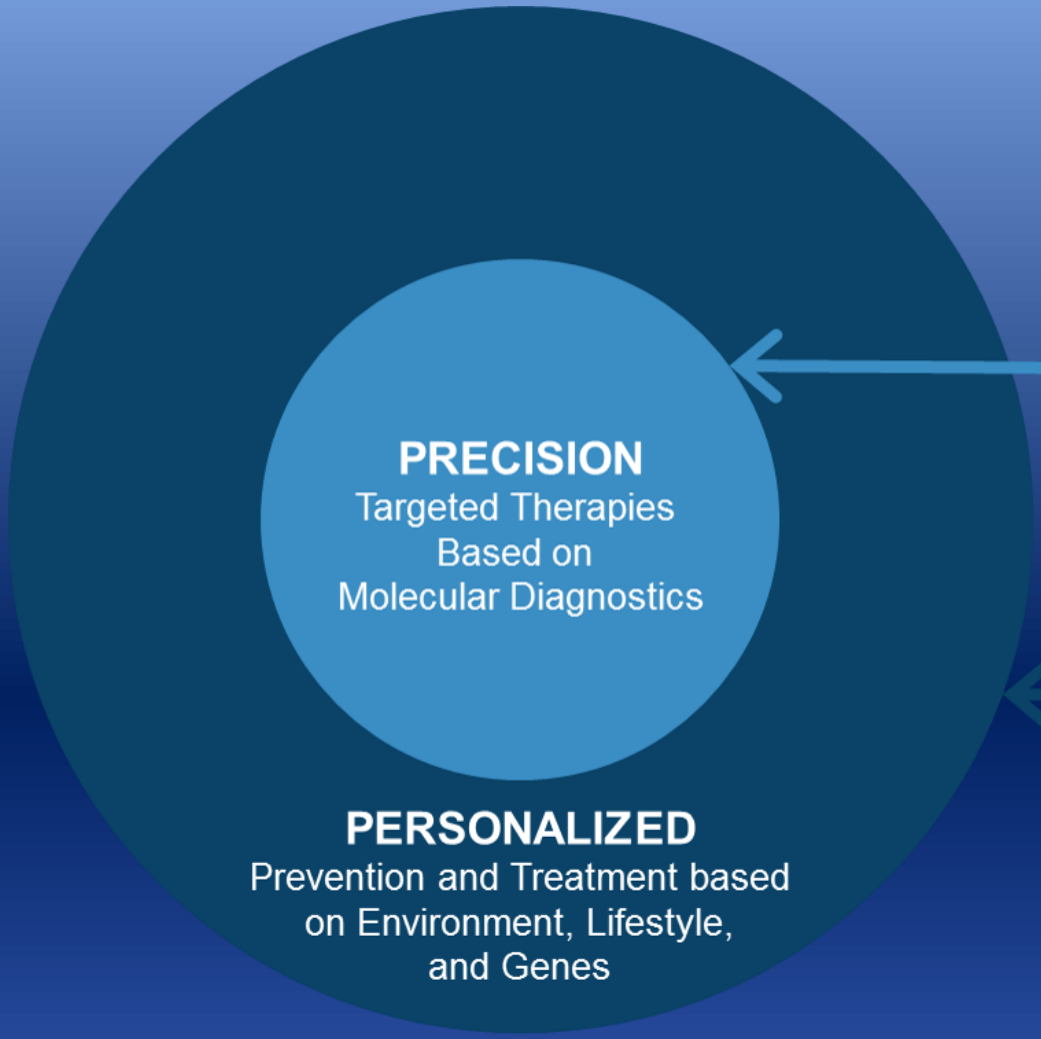
One size DOESN'T fit all

(i.e. Breast Cancer Screening)




Current Medicine
One Treatment Fits All
Cancer patients with
e.g. colon cancer
Therapy
Effect
No effect
Adverse effects
Future Medicine
More Personalized Diagnostics
Cancer patients with
e.g. colon cancer
Blood, DNA,
Urine and Tissue Analysis
Therapy
Effect


WHAT?
Personalized Medicine
HOW?
Precision Medicine
WHY?
Deliver the right
health intervention



Precision Medicine
is science – a new wave of evidence-based medicine

Personalized Medicine
is a practice – managing a patient's care more holistically

Review > Nat Rev Clin Oncol. 2018 May;15(5):292-309. doi: 10.1038/nrclinonc.2018.30. Epub 2018 Feb 27.

Epigenome-based cancer risk prediction: rationale, opportunities and challenges

Risk-tailored early diagnostic and/or primary prevention strategies are urgently required.

The ideal risk-predictive test should:

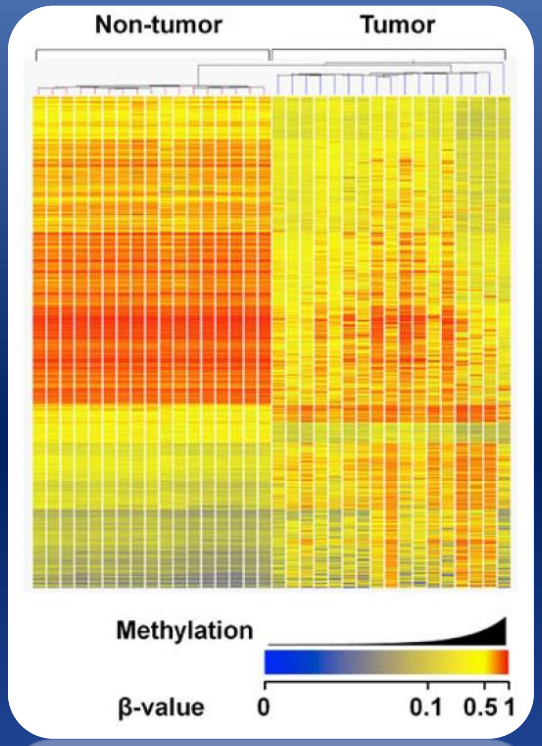
1. Integrate the effects of both genetic and nongenetic factors
2. Aim to capture these effects using an approach that is both biologically stable and technically reproducible;
3. Derive a score from easily accessible biological samples that acts as a surrogate for the organ in question
4. Enable the effectiveness of risk-reducing measures to be monitored.

Epigenome and, in particular, DNA methylation-based tests meet all of these requirements

Considerable challenges - The cell type specificity of DNA methylation and the extensive cellular heterogeneity of the easily accessible surrogate cells that might contain information relevant to less accessible tissues

Genome-wide DNA methylation analysis in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the one of the most common cancers and lethal diseases in the world (3rd). 2.2 billion of people infected by HBV/HCV, counting 5 million of deaths/yr



nature COMMUNICATIONS

Clinical cytology biobank archival samples. *The Clinical Cytology biobank at the Karolinska University Laboratory, Karolinska University Hospital, systematically stores a compacted aliquot of all* ***ThinPrep liquid-based cytology samples taken as part of the organised cervical screening programme***

ARTICLE

https://doi.org/10.1038/s41467-021-26615-y OPEN

Check for updates

The DNA methylome of cervical cells can predict the presence of ovarian cancer

James E. Barrett[1,2,3], Allison Jones[3], Iona Evans[3], Daniel Reisel[3], Chiara Herzog[1,2], Kantaraja Chindera[3], Mark Kristiansen[4], Olivia C. Leavy[5,6], Ranjit Manchanda[7,8,9], Line Bjørge[10,11], Michal Zikan[12,13], David Cibula[13] & Martin Widschwendter[1,2,3,14]✉

The vast majority of epithelial ovarian cancer arises from tissues that are embryologically derived from the Müllerian Duct. Here, we demonstrate that a DNA methylation signature in easy-to-access Müllerian Duct-derived cervical cells from women with and without ovarian cancer (i.e. referred to as the Women's risk IDentification for Ovarian Cancer index or WID-OC-index) is capable of identifying women with an ovarian cancer in the absence of tumour DNA with an AUC of 0.76 and women with an endometrial cancer with an AUC of 0.81. This and the observation that the cervical cell WID-OC-index mimics the epigenetic program of those cells at risk of becoming cancerous in BRCA1/2 germline mutation carriers (i.e. mammary epithelium, fallopian tube fimbriae, prostate) further suggest that the epigenetic mis-programming of cervical cells is an indicator for cancer predisposition. This concept has the potential to advance the field of risk-stratified cancer screening and prevention.

ARTICLE

https://doi.org/10.1038/s41467-021-27918-w OPEN

Check for updates

The WID-BC-index identifies women with primary poor prognostic breast cancer based on DNA methylation in cervical samples

James E. Barrett[1,2,3,18], Chiara Herzog[1,3,18], Allison Jones[2], Olivia C. Leavy[4,5], Iona Evans[2], Susanne Knapp[2], Daniel Reisel[2], Tatiana Nazarenko[2], Yoo-Na Kim[1,3], Dorella Franchi[6], Andy Ryan[2], Joanna Franks[7], Line Bjørge[8,9], Michal Zikan[10], David Cibula[11], Nadia Harbeck[12], Nicoletta Colombo[6,13], Frank Dudbridge[4,5], Louise Jones[14], Karin Sundström[15], Joakim Dillner[15], Angelique Flöter Rådestad[16], Kristina Gemzell-Danielsson[16], Nora Pashayan[17] & Martin Widschwendter[1,2,3,16]✉

[…] Utilising cervical liquid-based cytology samples, we develop the DNA methylation-based Women's risk IDentification for Breast Cancer index (WID-BC-index) that identifies women with breast cancer with an AUROC (Area Under the Receiver Operator Characteristic) of 0.84 (95% CI: 0.80–0.88) and 0.81 (95% CI: 0.76–0.86) in internal and external validation sets, respectively. CpGs at progesterone receptor binding sites hypomethylated in normal breast tissue of women with breast cancer or in BRCA mutation carriers are also hypomethylated in cervical samples of women with poor prognostic breast cancer. Our data indicate that a systemic epigenetic programming defect is highly prevalent in women who develop breast cancer. Further studies validating the WID-BC-index may enable clinical implementation for monitoring breast cancer risk.

Biology of Human Tumors

Clinical Cancer Research

Integrated Epigenomics Analysis Reveals a DNA Methylation Panel for Endometrial Cancer Detection Using Cervical Scrapings

Rui-Lan Huang[1], Po-Hsuan Su[2], Yu-Ping Liao[3], Tzu-I Wu[3,4], Ya-Ting Hsu[5], Wei-Yu Lin[6], Hui-Chen Wang[3], Yu-Chun Weng[2], Yu-Che Ou[7], Tim Hui-Ming Huang[5,8], and Hung-Cheng Lai[1,2,3,9]

180 methylated genes, which constituted four consensus clusters. Serial testing of tissues and cervical scrapings detected 14 genes that are hypermethylated in endometrial cancer. Three genes, BHLHE22, CDO1, and CELF4, had the best performance. Individual genes were sensitivity of 83.7%–96.0% and specificity of 78.7%–96.0%. A panel comprising any two of the three hypermethylated genes reached a sensitivity of 91.8%, specificity of 95.5%, and odds ratio of 236.3 (95% confidence interval, 56.4–989.6). These markers were also applied to cervical scrapings of type II endometrial cancer patients, and detected in 13 of 14 patients.

Conclusions: This study demonstrates the potential use of methylated BHLHE22/CDO1/CELF4 panel for endometrial cancer screening of cervical scrapings.

J Gynecol Oncol. 2018 Jan;29(1):e17
https://doi.org/10.3802/jgo.2018.29.e17
pISSN 2005-0380·eISSN 2005-0399

JGO JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

The feasibility of detecting endometrial and ovarian cancer using DNA methylation biomarkers in cervical scrapings

Cheng-Chang Chang,[1] Hui-Chen Wang,[2] Yu-Ping Liao,[3] Yu-Chih Chen,[4] Yu-Chun Weng,[3] Mu-Hsien Yu,[1] Hung-Cheng Lai[2,3]

[1]Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[2]Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei Medical University, New Taipei, Taiwan
[3]Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[4]Division of Research and Analysis, Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan

OPEN ACCESS

Tissues of EC/normal endometrium, OC/normal ovary, were verified in training set using cervical scrapings of 10 EC/10 OC patients and 10 controls, and further validated in the testing set using independent cervical scrapings in 30 EC/30 OC patients and 30 controls. We generated cut-off values of methylation index (M-index) from cervical scrapings to distinguish between cancer patients and control. Sensitivity/specificity of DNA methylation biomarkers in detecting EC and OC was calculated.

Results: Of 14 genes, 4 (PTGDR, HS3ST2, POU4F3, MAGI2) showed hypermethylation in EC and OC tissues. POU4F3 and MAGI2 exhibited hypermethylation in training set were validated in independent cases. The mean M-index of POU4F3 is 78.28 in EC and 20.36 in OC, which are higher than that in controls (6.59; $p<0.001$ and $p=0.100$, respectively), and that of MAGI2 is 246.0 in EC and 12.2 in OC, which is significantly higher that than in controls (2.85; $p<0.001$ and $p=0.480$, respectively).
Sensitivity and specificity of POU4F3/MAGI2 were 83%–90% and 69%–75% for detection of EC, and 61% and 62%–69% for the detection of OC.
Conclusion: potential of EC/OC detection through testing for DNA methylation in cervical scrapings.

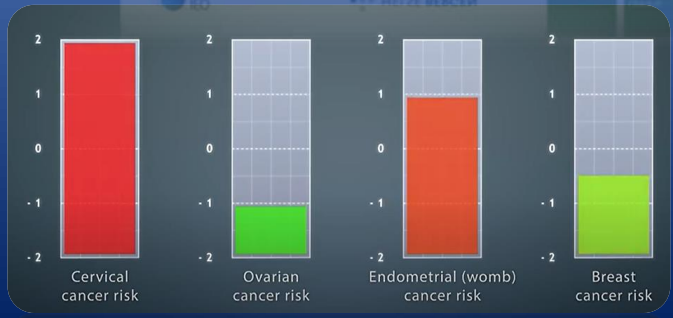
the eve appeal

The Eve Appeal is the leading UK national charity funding research and raising awareness into the five gynaecological cancers – womb, ovarian, cervical, vulval and vaginal.

A screening programme to provide one test for four cancers

The Eve Appeal launched a ground-breaking four year European-wide research programme in September 2015 which has been partly funded by the European Commission (Horizon 2020) and led by UCL Women's Cancer Department. The vision of FORECEE (4C) is to develop a screening test that aims to prevent four cancers- breast, womb, ovarian and cervical.

The first results from the FORECEE programme, published in Nature Communications, show promising results- the test (called the WID-Test) was able to detect up to 30% more women with breast and ovarian cancer than current genetic-based tests.



IEO Istituto Europeo di Oncologia

TROVA UN MEDICO | PRENOTA UNA VISITA | RAGGIUNGICI | CONTATTACI | AREA PERSONALE

CHI SIAMO | PER I PAZIENTI | PREVENZIONE | RICERCA | FORMAZIONE | SCIENCE IN SOCIETY

Un istituto di riferimento dove la ricerca sui tumori diventa cura in tempo reale

Home » PER I PAZIENTI » Sperimentazioni cliniche » Novità » Studio Forecee

FORECEE: un test unico per tutti i tumori della donna

4C forecee Four cancers One test

Lo IEO è l'unico centro italiano a partecipare al programma FORECEE, il più ampio studio per la prevenzione dei tumori femminili mai realizzato in Europa. Il pap test come screening anche per seno, ovaio ed endometrio.

nature COMMUNICATIONS

Clinical cytology biobank archival samples. *The Clinical Cytology biobank at the Karolinska University Laboratory, Karolinska University Hospital, systematically stores a compacted aliquot of all* ***ThinPrep liquid-based cytology samples taken as part of the organised cervical screening programme***

Possibilità di screening **"Taylored"** su categorie a rischio

Opportunità diagnostica

Possibilità di utilizzare buona metodica di screening già in essere

Ottimizzazione risorse dei sistemi sanitari pubblici (COVID-19 lesson!)

Grazie per l'attenzione!