Costa Rican
Research Center on Surgery and Cancer

Bridging the gap between basic and applied cancer research

Prof. Dr. Rodrigo Mora, Ph.D.
Director CICICA-UCR

Ricardo Chinchilla
Ph.D. candidate

Ana Cristina Castro
Ph.D candidate

CICICA
Centro de
Investigación en
Cirugía y Cáncer

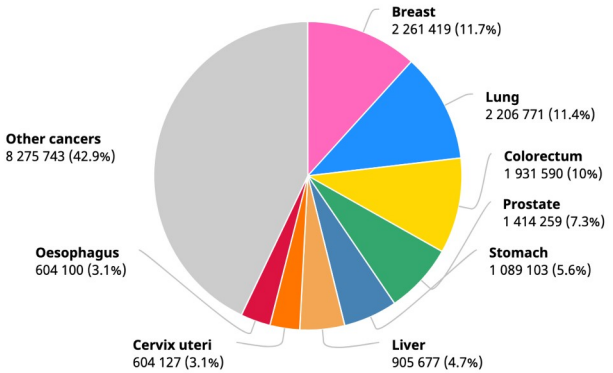
UNIVERSIDAD DE COSTA RICA

1

World

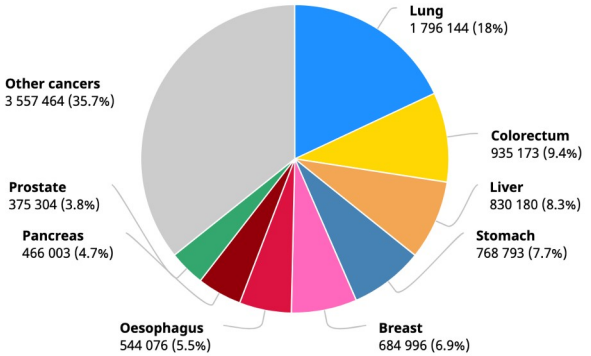
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



Total: 9 958 133 deaths

Geography

Numbers at a glance

Total population

7 794 798 844

Number of new cases

19 292 789

Number of deaths

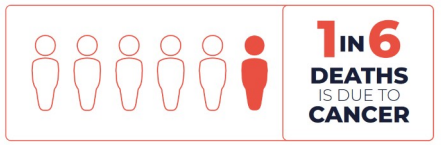
9 958 133

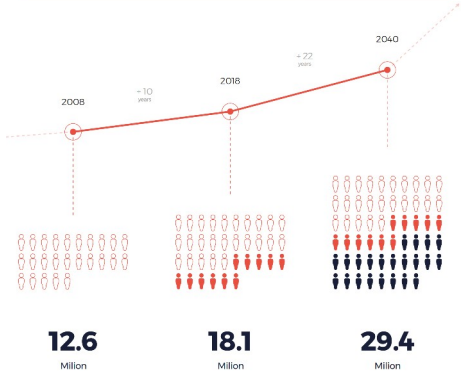
Number of prevalent cases (5-year)

50 550 287

2

The global cancer burden is significant and increasing





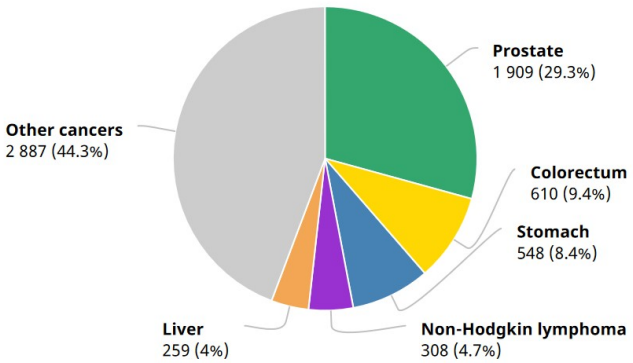
Physical, emotional and financial burden for individuals, their families, communities, health systems and governments

[1] **The Global Cancer Observatory, 2020**. gco.iarc.fr. & [2] **WHO report on cancer 2020**. ISBN 978-92-4-000129-9

Costa Rica

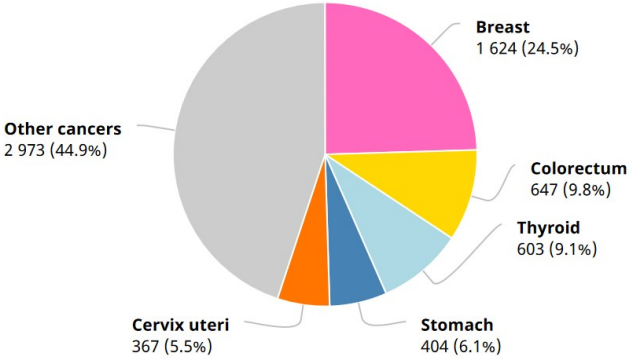
Source: Globocan 2020

Number of new cases in 2020, males, all ages



Total: 6 521

Number of new cases in 2020, females, all ages



Geography

Numbers at a glance

Total population

5 094 114

Number of new cases

13 139

Number of deaths

6 028

Number of prevalent cases (5-year)

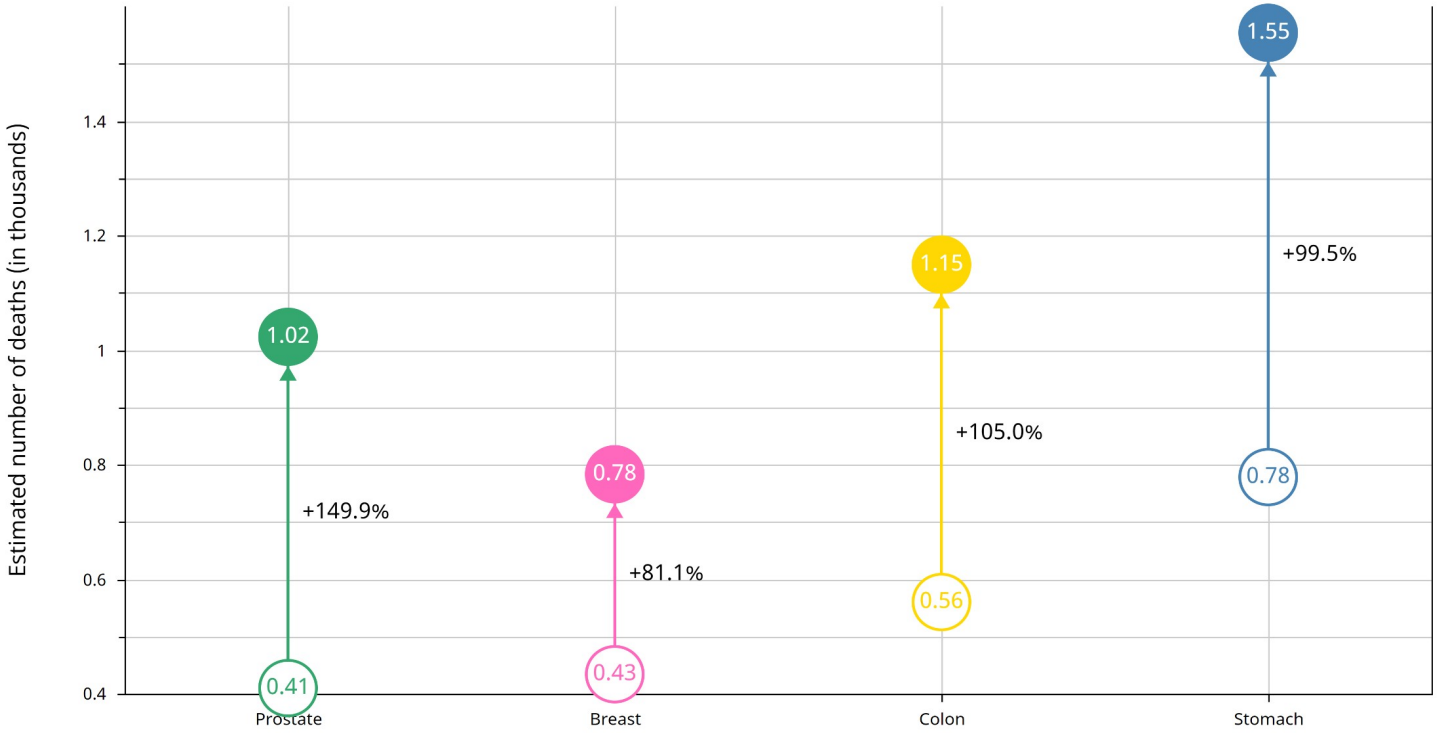
35 534

[1] **The Global Cancer Observatory, 2020**. gco.iarc.fr. & [2] **Instituto Nacional de Estadística y Censos**. inec.cr

Cancer in Costa Rica

Estimated number of deaths from 2020 to 2040, Both sexes, age [0-85+]
Costa Rica

GLOBAL CANCER OBSERVATORY

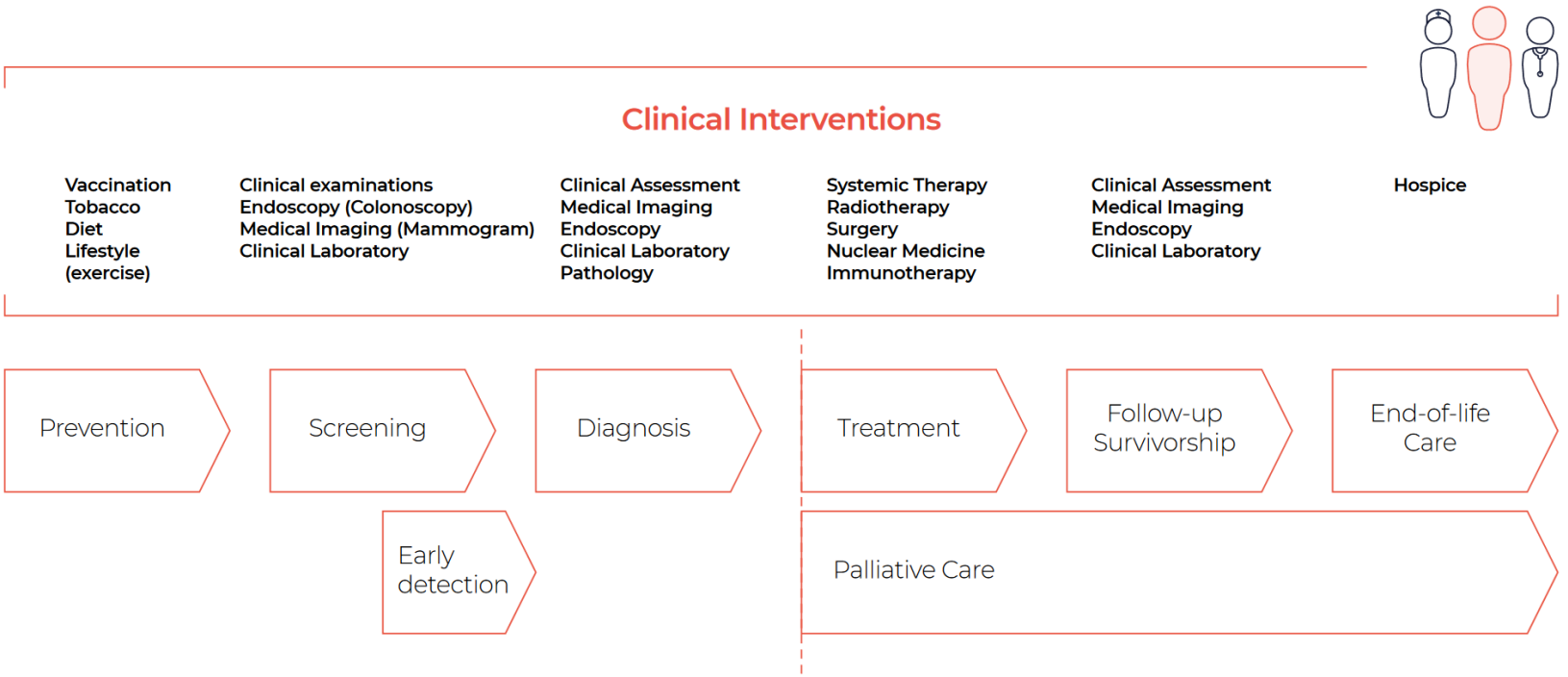


International Agency for Research on Cancer
World Health Organization

UCR
UNIVERSIDAD DE COSTA RICA

Spectrum of cancer control interventions

Figure i.1. Interventions along the cancer continuum and examples of levels of care.



WHO: prioritize in prevention and early diagnosis

WHO report on cancer 2020. Setting priorities, investing wisely and providing care for all. ISBN 978-92-4-000129-9

Research Center on Surgery and Cancer

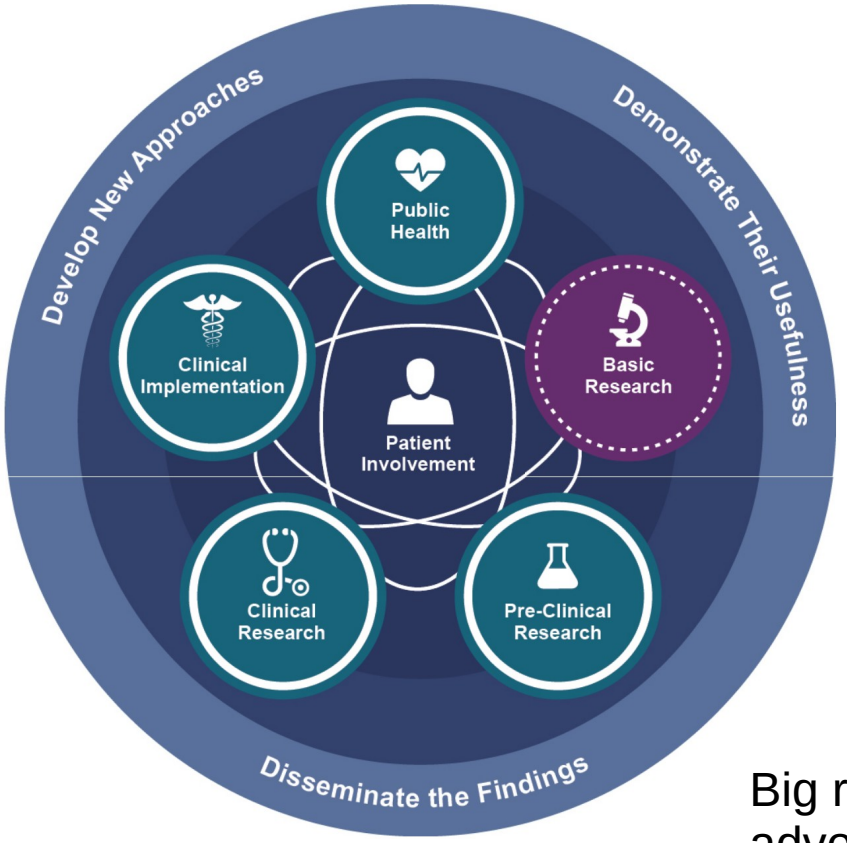
(Inaugurated in February 2023)

Interdisciplinary unit dedicated to basic and applied research on surgery and cancer

(Interdisciplinary: health sciences, basic sciences, veterinary medicine, engineering, …)

Focus on research, development and implementation of new strategies and methodologies for cancer prevention, early diagnosis and precision oncology

Translational medicine perspective approach



Big role of patient advocates!

Combining the findings from basic-, applied- and clinical research to build upon and inform each other, in order to develop projects that translate into a significant, positive impact on the population's health..

ncats.nih.gov/translation/spectrum

Research Center facilities

- Specialized clinic for early cancer diagnosis and precision oncology

- Program on continued education and training on minimally invasive surgery

- Specialized laboratory for early cancer diagnosis and precision oncology

1) Specialized clinic for early cancer diagnosis and precision oncology

- Medical care models for early detection and diagnosis of cancer

- Intended to tackle the most relevant cancers in our country
(prostate, testicle, cervix, ovary, breast, oropharynx, thyroid, esophagus, stomach, colorectum, liver, bile duct, pancreas)

- Medical offices staffed by medical specialists in gynecologic oncology, urology, head and neck, thyroid cancer, etc & Endoscopy unit for Gastroenterology

- Partnership with civil society cancer organizations Foro permanente de Cáncer en Mujeres de Costa Rica

- Specific agreements with the Costa Rican Social Security Fund (aka CCSS)(which is responsible for the public universal health care system of our country)

Specialists at CICICA

Dr. Angie Mora, Ginecology-Oncology

Dr. Gonzalo Azua, Urologist

2) Program on continued education and training on minimally invasive surgery

Training process through:

- simulation **(Laparoscopic Simulators)**
- practice in an *in vivo* model in a controlled surgical environment **(Operating Room)**

Aimed at

- medical specialists

- postgraduate students in medical specialties (residents) in the surgical area

- postgraduate students in surgical nursing

Development of complex surgical skills

Continued education and training on:

- Laparoscopy (basic, intermediate, advanced)
- Microsurgery
- Laparoscopic surgical instrumentation
- Specific advanced laparoscopy courses

Dr. Marco Zúñiga, Specialist in Non-Invasive Surgery

Dr. Jilma Alemán, Veterinarian

3) Specialized laboratory for early cancer diagnosis and precision oncology

- Establishment of cellular, molecular, immunological and pathological laboratory tests for precision oncology

Precision oncology: an approach that takes into account differences in each person's genes, environment, and lifestyles to tailor cancer prevention and treatment.

- Clinical research projects*

Projects on new diagnostic tools in cancer

*Adherence to national and international clinical research law and regulations, and ethical review boards.

Drug bioequivalence studies

Early cancer screening in a high risk population for colon and gastric cancer.

cancer.gov

- Facilities under one roof:

  - Cell culture
  - Clinical pathology
  - Molecular biology
  - Flow cytometry
  - Image flow cytometry
  - Next generation sequencing (NGS)
  - Single-cell sequencing
  - Circulating tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs)

Ricardo Chinchilla
Microbiologist

Ana Cristina
Microbiologist

Jad Abaas,
Pathologist

- Basic and applied research projects

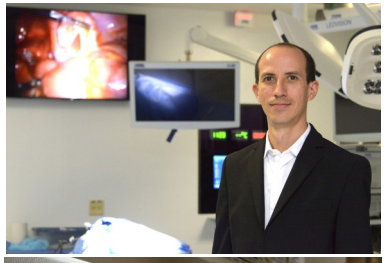
- Research core facility

- Diagnostic services for cancer

Basic Research

Mechanisms of tumor chemosensitivity

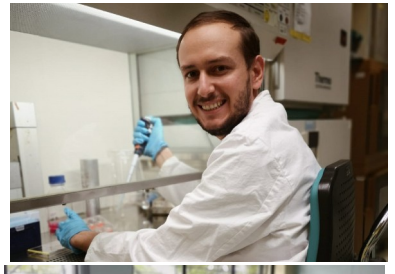
-Late biological responses to pulsed - low dose genotoxic chemotherapeutic agents.
-Gene dosage compensation in a model of accelerated genomic instability



Dr. Steve Quirós, Ph.D.

Oncoimmunology

-Tumor-specific T cell receptors as a therapeutic application against cancer.



Dr. Isaac Quirós, Ph.D.

-Modulation of immunogenic cell death and effect on bystander cells.
-Chemokine interaction network and predictive models of chemotatic effect.

Dr. Javier Mora, Ph.D.

Tumor microenvironment

-Role of *Helicobacter pylori* in the microenvironment that supports the emergence of gastric cancer.
-Research platform for the epidemiology and biology of colorectal cancer in Costa Rica.

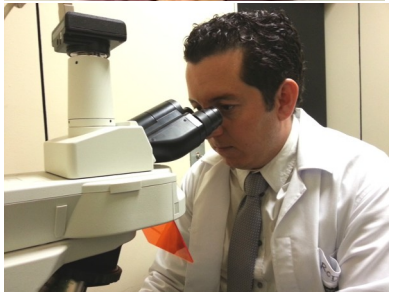
Dr. Warner Alpízar, Ph.D.

Systems Biology of Cancer

-Gene dosage compensation in aneuploid cancer.

-Bistability in Macrophage Polarization.

-miRNA-based therapeutics.



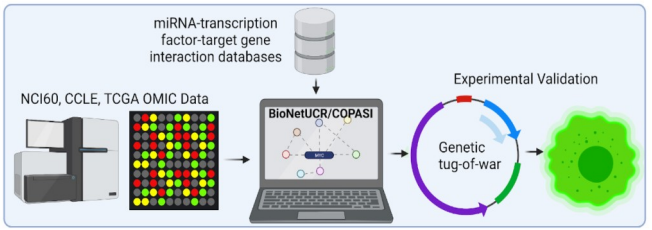
Dr. Rodrigo Mora, Ph.D.

Targeting Gene dosage compensation in aneuploid cancer

iScience

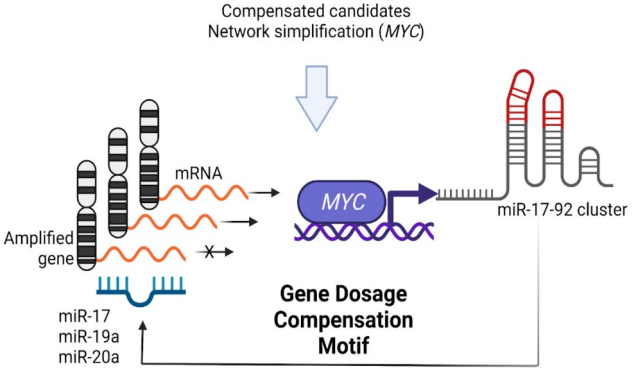
Available online 8 November 2021, 103407

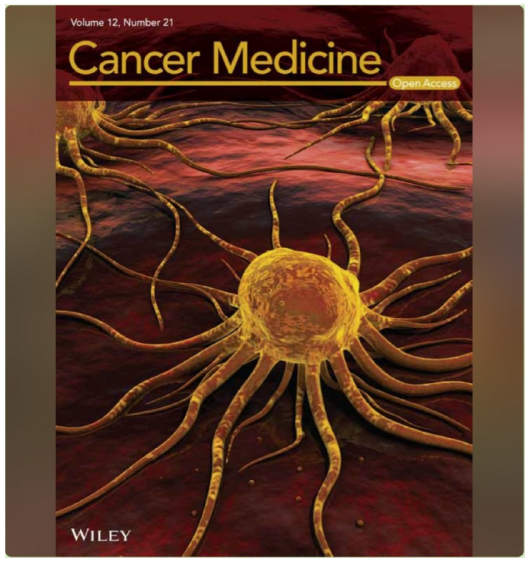
In Press, Journal Pre-proof



Article

MYC dosage compensation is mediated by miRNA-transcription factor interactions in aneuploid cancer





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DOI: 10.1002/cam4.6719

Cancer Medicine Open Access WILEY

REVIEW

Gene dosage compensation: Origins, criteria to identify compensated genes, and mechanisms including sensor loops as an emerging systems-level property in cancer

Diana M. Bravo-Estupiñan[1,2,3,4] | Karol Aguilar-Guerrero[1,5] | Steve Quirós[1,6] | Man-Sai Acón[1] | Christian Marín-Müller[4] | Miguel Ibáñez-Hernández[3] | Rodrigo A. Mora-Rodríguez[1,6]

Translational Research and implementation of novel diagnostics

- Diagnostic tests in anatomical and clinical pathology

Image Analysis and Machine learning

- Diagnostic test development and implementation

e.g. detection of HPV malignant transformation and image based assays

- Genetic testing for hereditary cancer predisposition syndromes & for somatic variants or mutations in tumors & Pharmacogenomics

- Liquid biopsy (ctDNA and CTCs) and exome sequencing

e.g. ctDNA and CTCs as a predictor of response to treatment in breast cancer

- Prospective OncoSeek study on a high risk population for Colon and Gastric Cancer.

Translational genomic research on genetic biomarkers in Liquid Biopsy

Dr. Ricardo Chinchilla, M.Sc.

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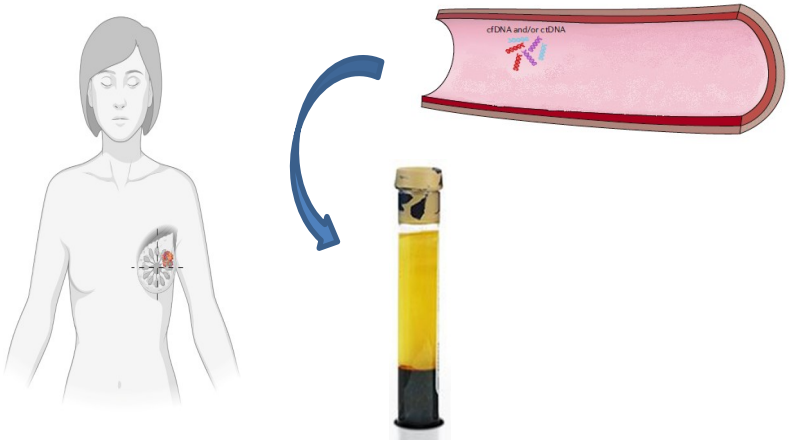
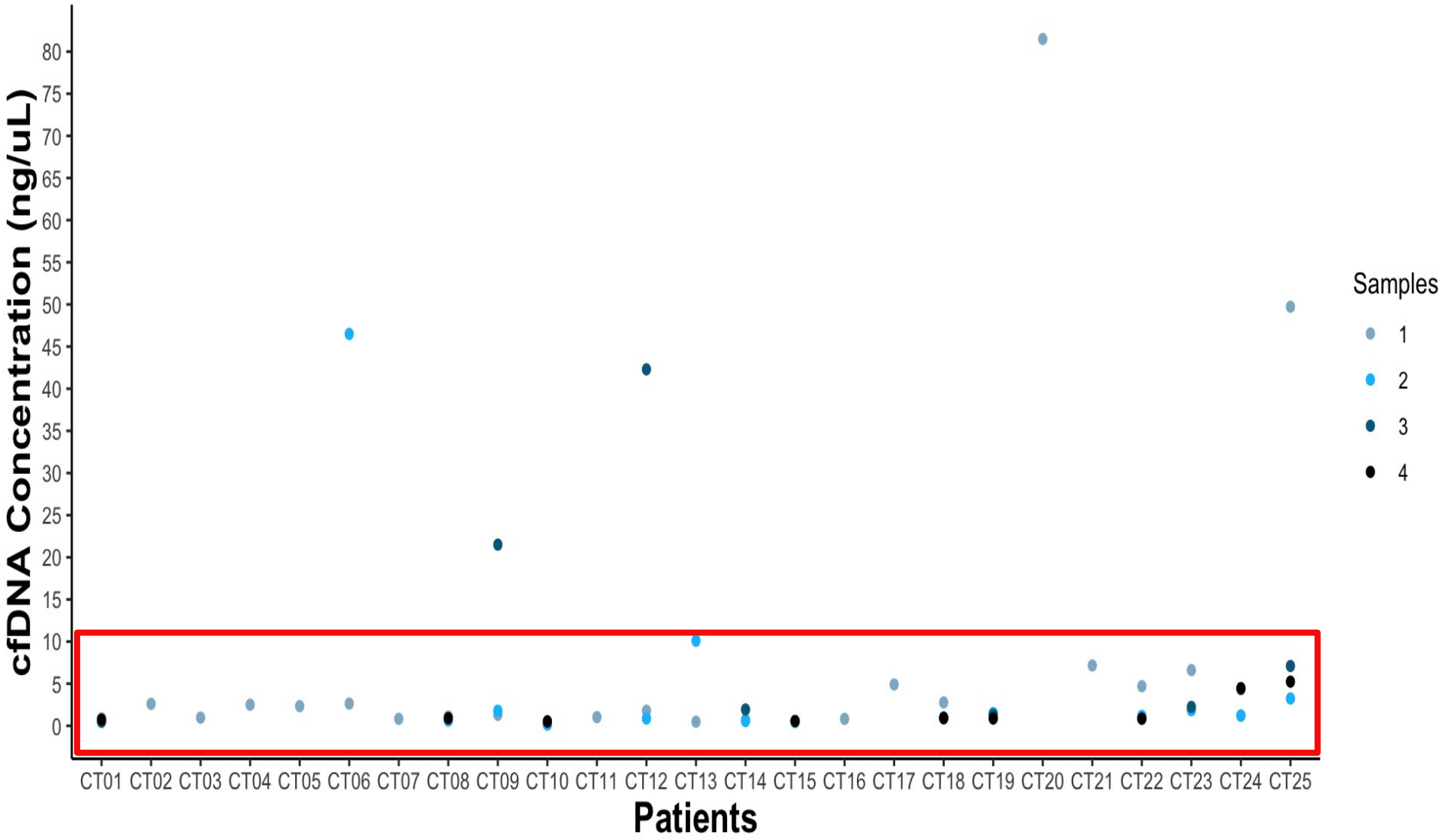
- Genetic biomarkers of Circulating Tumor DNA for Monitoring Breast Cancer Patients in Costa Rica
  - Prospective study: 1 to 4 blood samples
  - cfDNA concentration
  - SNVs:
    - *ESR1*: Y537N, Y537S, Y537C y D538G
    - *PIK3CA*: E545K, H1047L

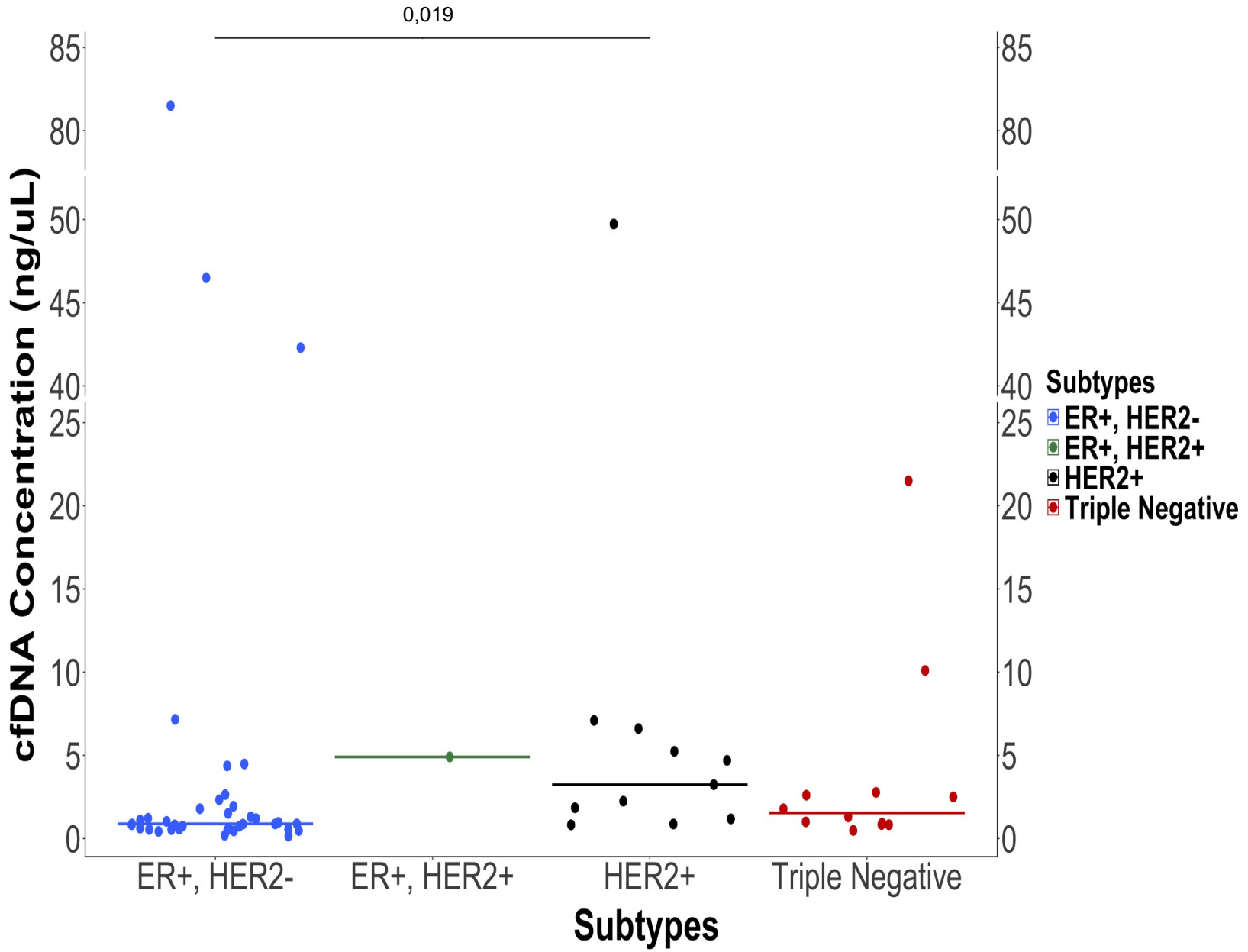
Dr. Allan Ramos PhD.



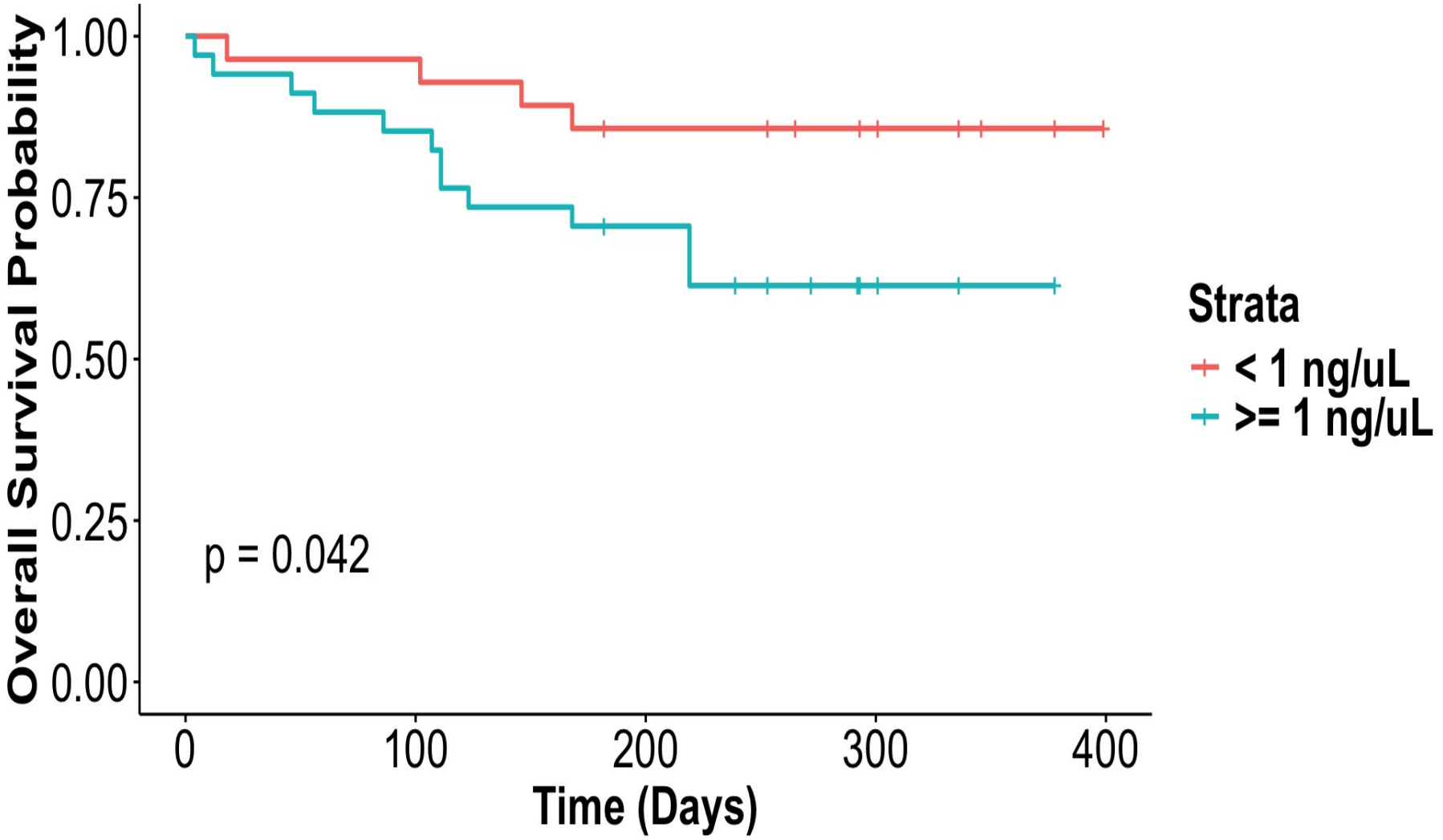
Results


cfDNA Concentration (ng/uL)
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
CT01 CT02 CT03 CT04 CT05 CT06 CT07 CT08 CT09 CT10 CT11 CT12 CT13 CT14 CT15 CT16 CT17 CT18 CT19 CT20 CT21 CT22 CT23 CT24 CT25
Patients
Samples
1
2
3
4

cfDNA in breast cancer subtypes



Overall Survival Probability according to cfDNA



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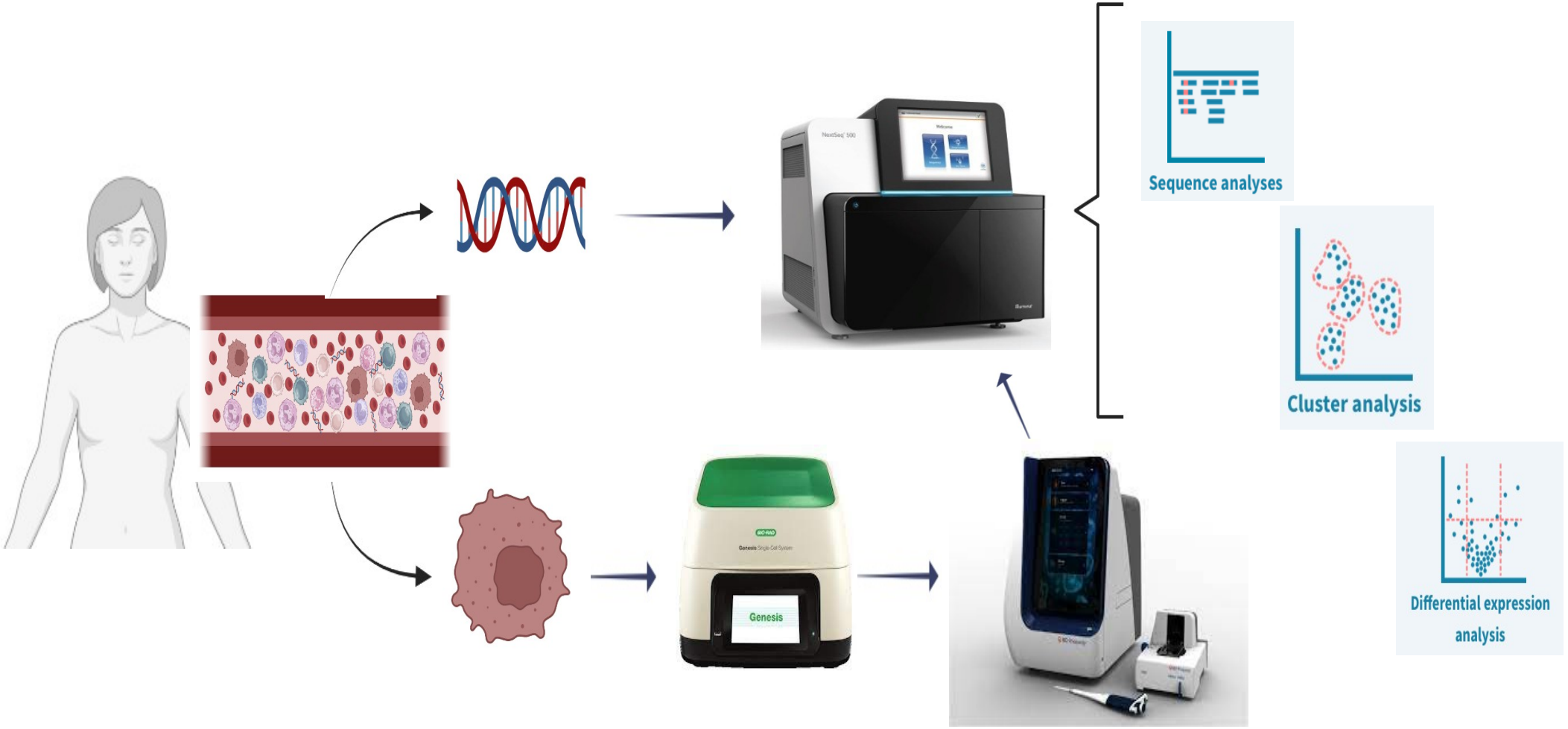
CICICA Centro de Investigación en Cirugía y Cáncer

- Dynamic levels of ctDNA and CTCs as a predictor of response or failure to combined therapy with Trastuzumab, Pertuzumab and Taxanes, in HER2-positive metastatic breast cancer from January 2024 to December 2026, in the Medical Oncology Services of San Juan de Dios, México, Calderón Guardia and San Vicente de Paúl Hospitals.



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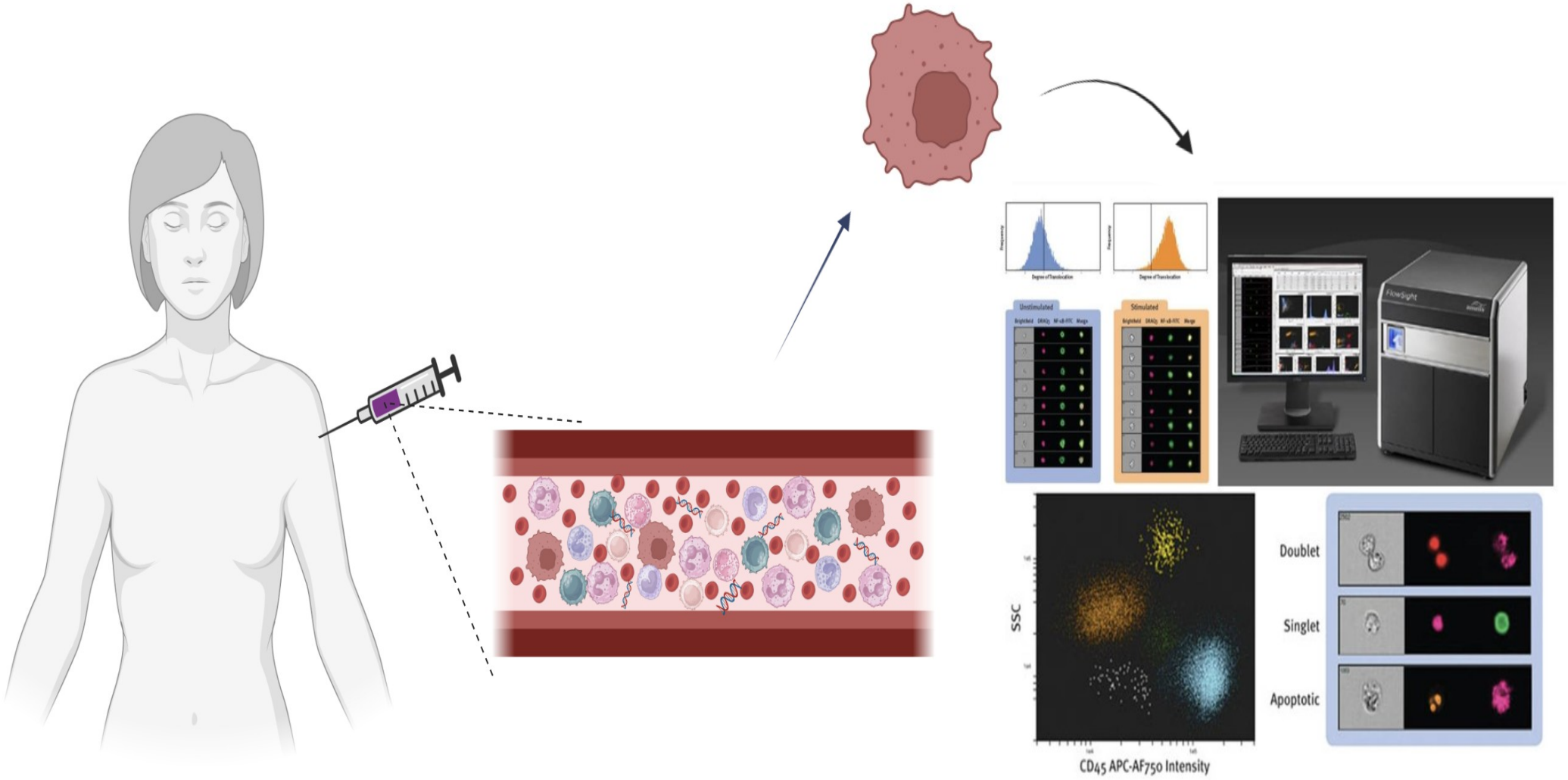
Ricardo Chinchilla Monge
ricardo.chinchilla_m@ucr.ac.cr

CICICA Centro de Investigación en Cirugía y Cáncer

- Protein biomarkers and analysis of images of circulating tumor cells (CTCs) in blood samples from patients with metastatic breast cancer.



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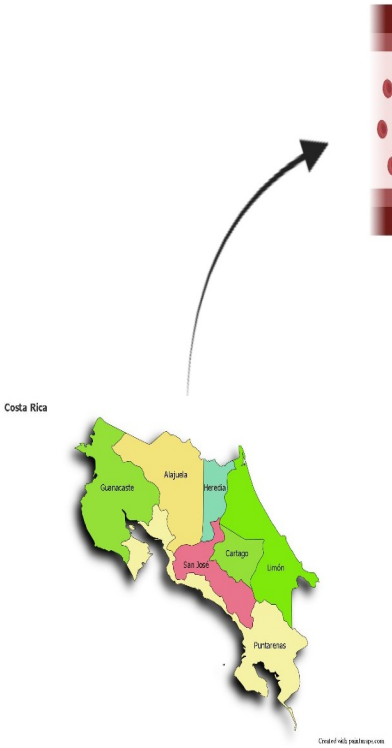
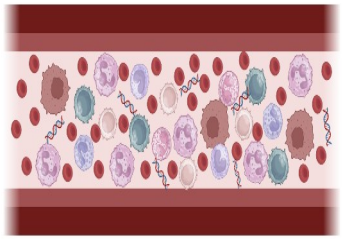
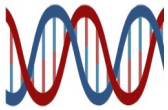
- Reference intervals for various biomarkers of circulating DNA in the Costa Rican in the Costa Rican population (IRAC Project)







Concentration (ng/µL)

-Integrity index
Alu sequences
-Alu methylation patterns
-Methylation porcentage

-ctDNA fragmentomics

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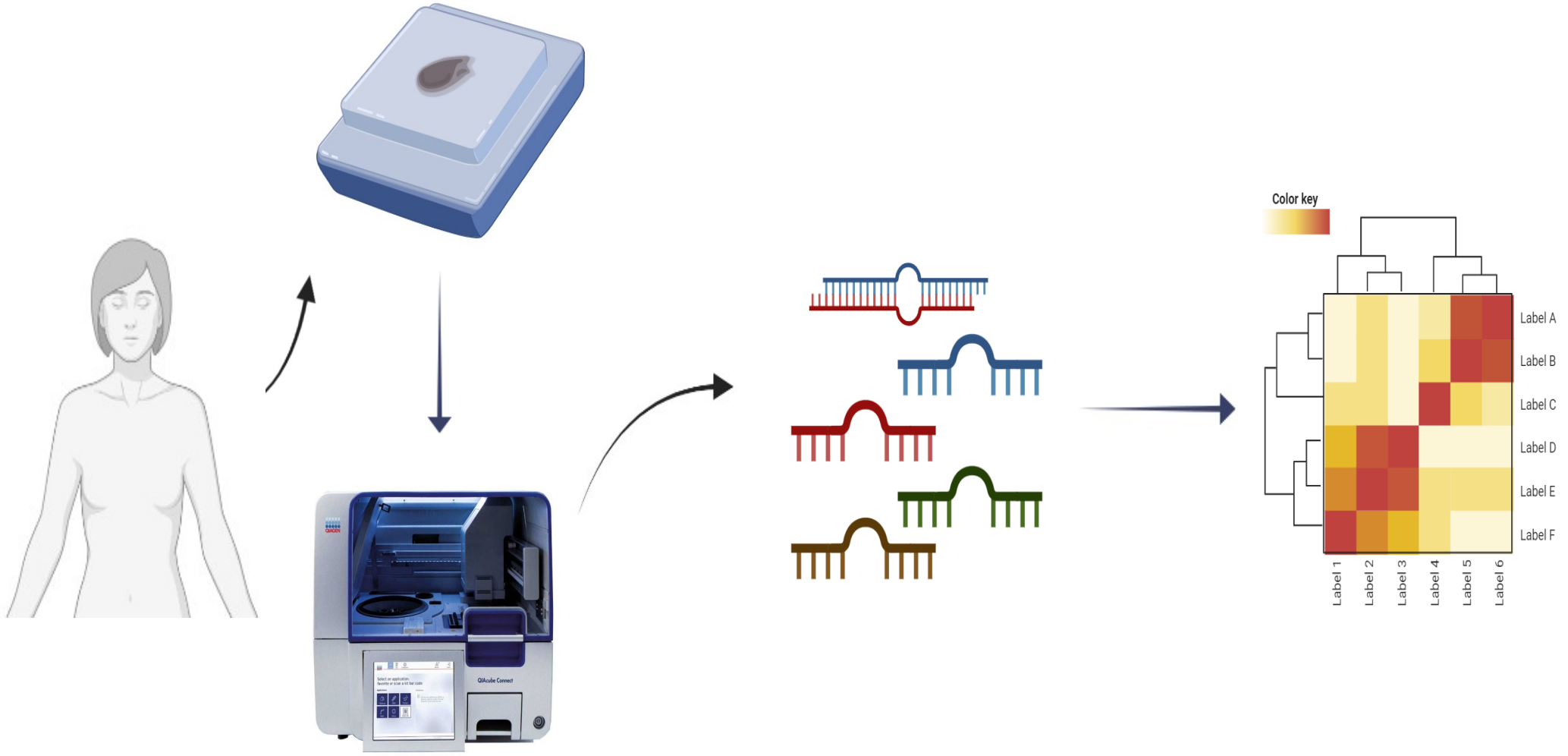
- Expression profile of microRNAs in paraffin-embedded tissue biopsies from breast cancer patients at Calderón Guardia Hospital during a one-year period.



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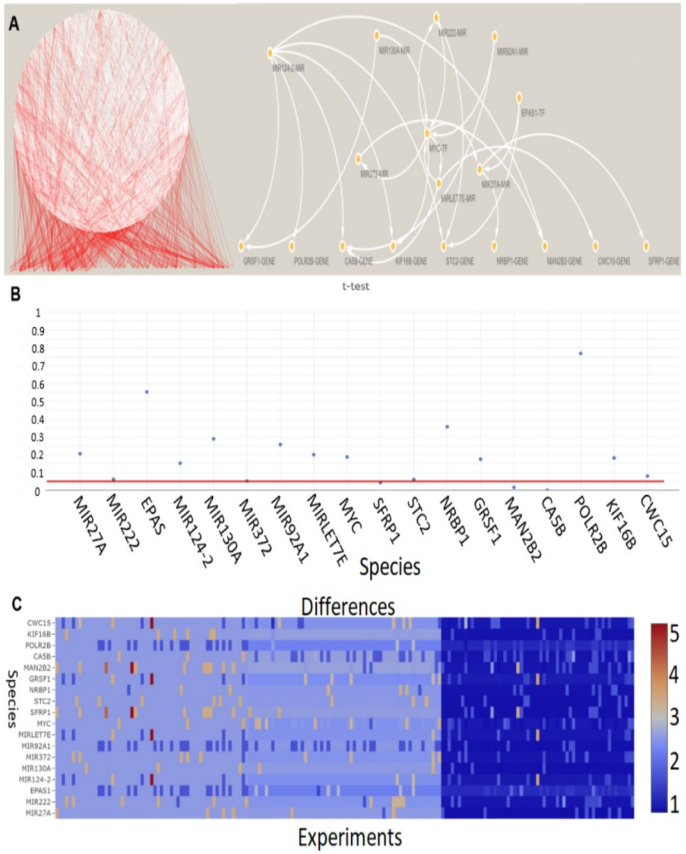
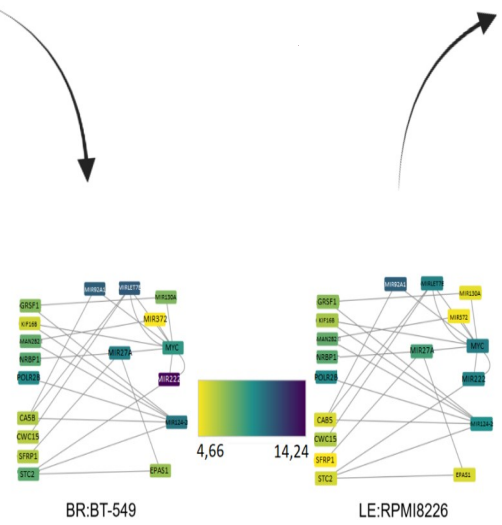
- Regulatory networks in the progression of ductal carcinoma in situ (DCIS) to invasive breast cancer (IBC).

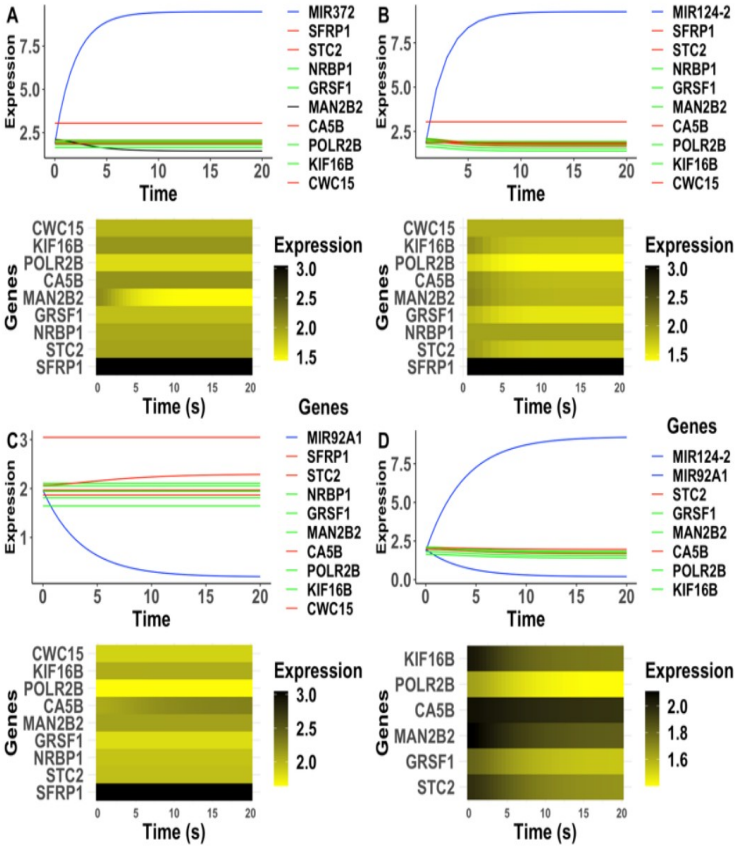
BioNetUCR

Cytoscape

COPASI
Complex Pathway Simulator



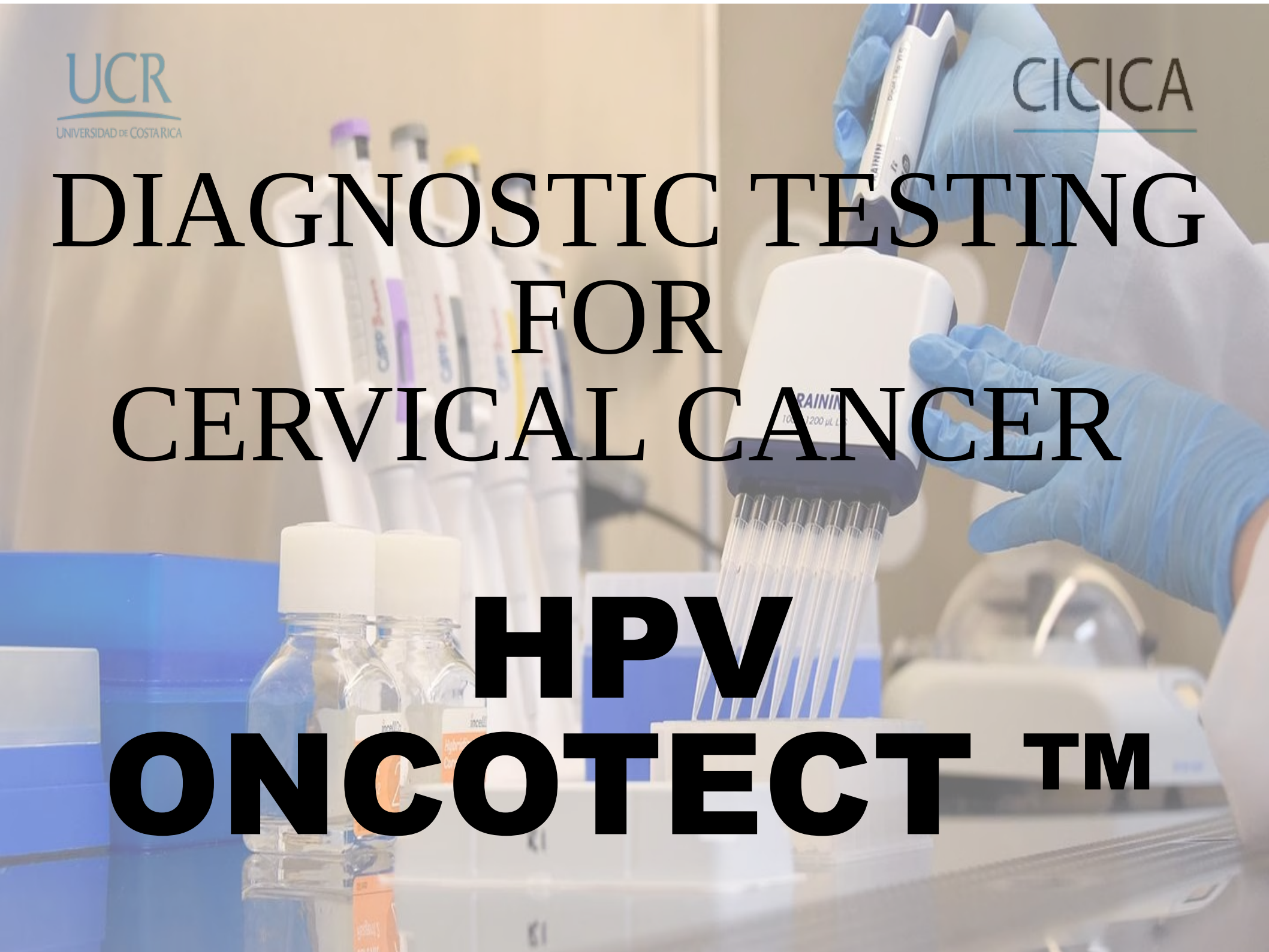




Ricardo, C. M., Noé, C. C., & Rodrigo, M. R. (2022, November). miR-124-2, miR-92-A1 and miR-372 regulate differential gene expression in a mathematical model of the progression of ductal carcinoma in situ (DCIS) to microinvasive breast cancer (MIBC). In *2022 IEEE 4th International Conference on BioInspired Processing (BIP)* (pp. 1-7). IEEE.

Translational cell biology research on image-enhanced cytology for cervical cancer

Dr. Ana Cristina Castro, M.Sc.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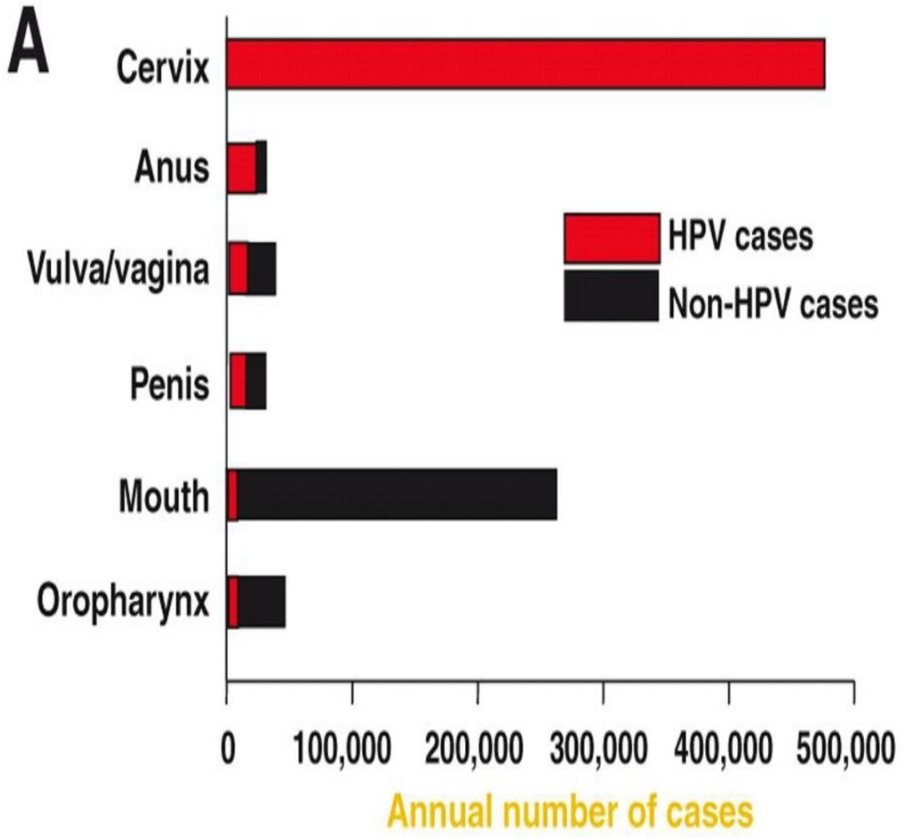
DIAGNOSTIC TESTING
FOR
CERVICAL CANCER
HPV
ONCOTECT ™

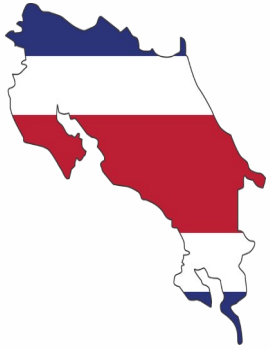
Human Papilloma Virus (HPV)

- Low risk HPV
- High risk HPV
    - Enters the cervical cells and has the capacity to cause carcinogenesis.



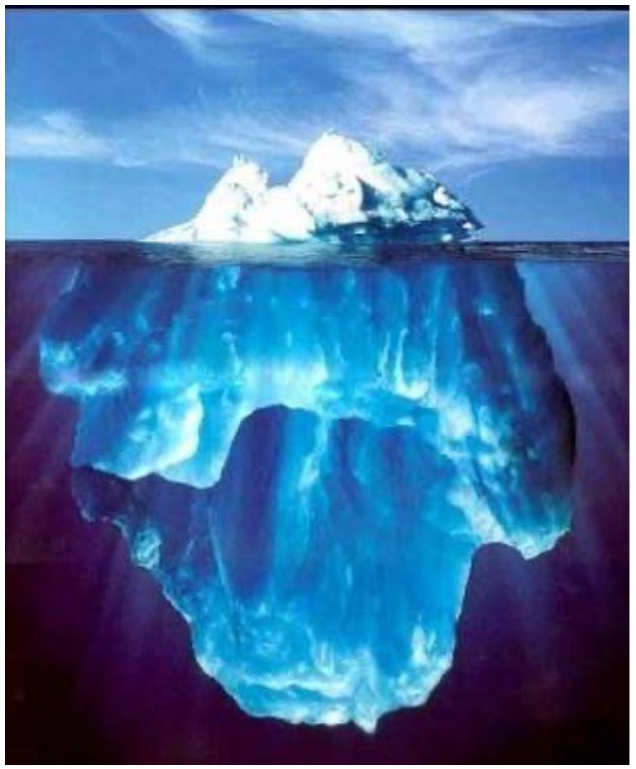
Cervical cancer

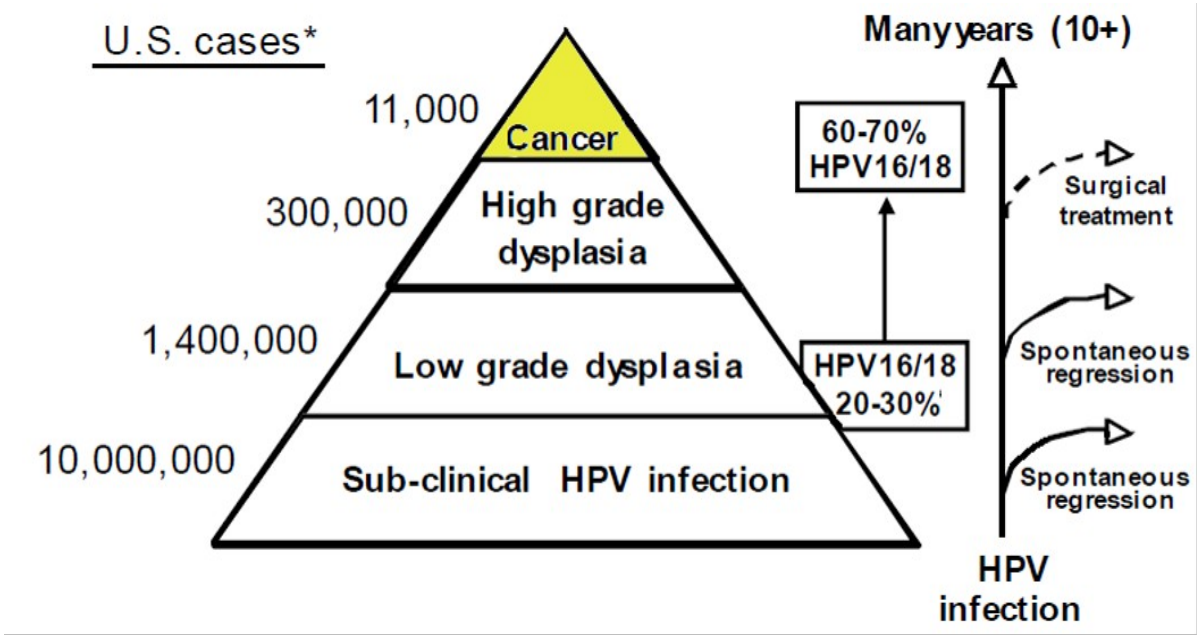
- 1st cause of death for women younger than 35 yo
- Mortality in low and middle income countries is 3x higher
- Worldwide a woman dies every **2 min**



- 4th cause of incidence and mortality due to cancer in women
- **320 cases per year with 140 deaths**

Cervical infection (and pathologies related to HPV)





Thousands of women are diagnosed with the viral infection but with high probability of spontaneous regression (virus elimination)

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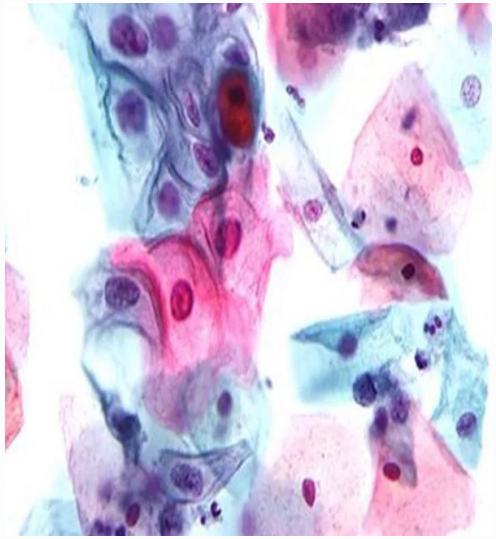
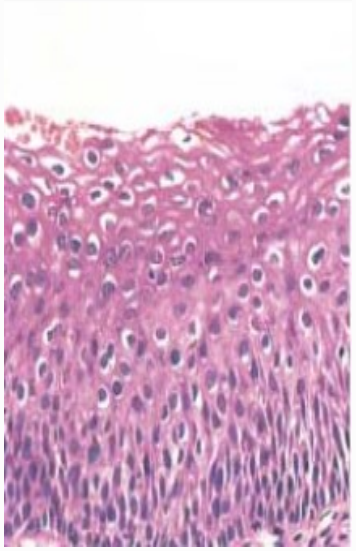
Detection is not the same as cancer

Triage and screening diagnostic tests



Pap

Bad sensitivity



Biopsy

Bad predictor of the disease!

Genotypes (hrHPV)

Low clinical sensitivity/specificity

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Screening

should have high sensitivity

Triage

should have high specificity

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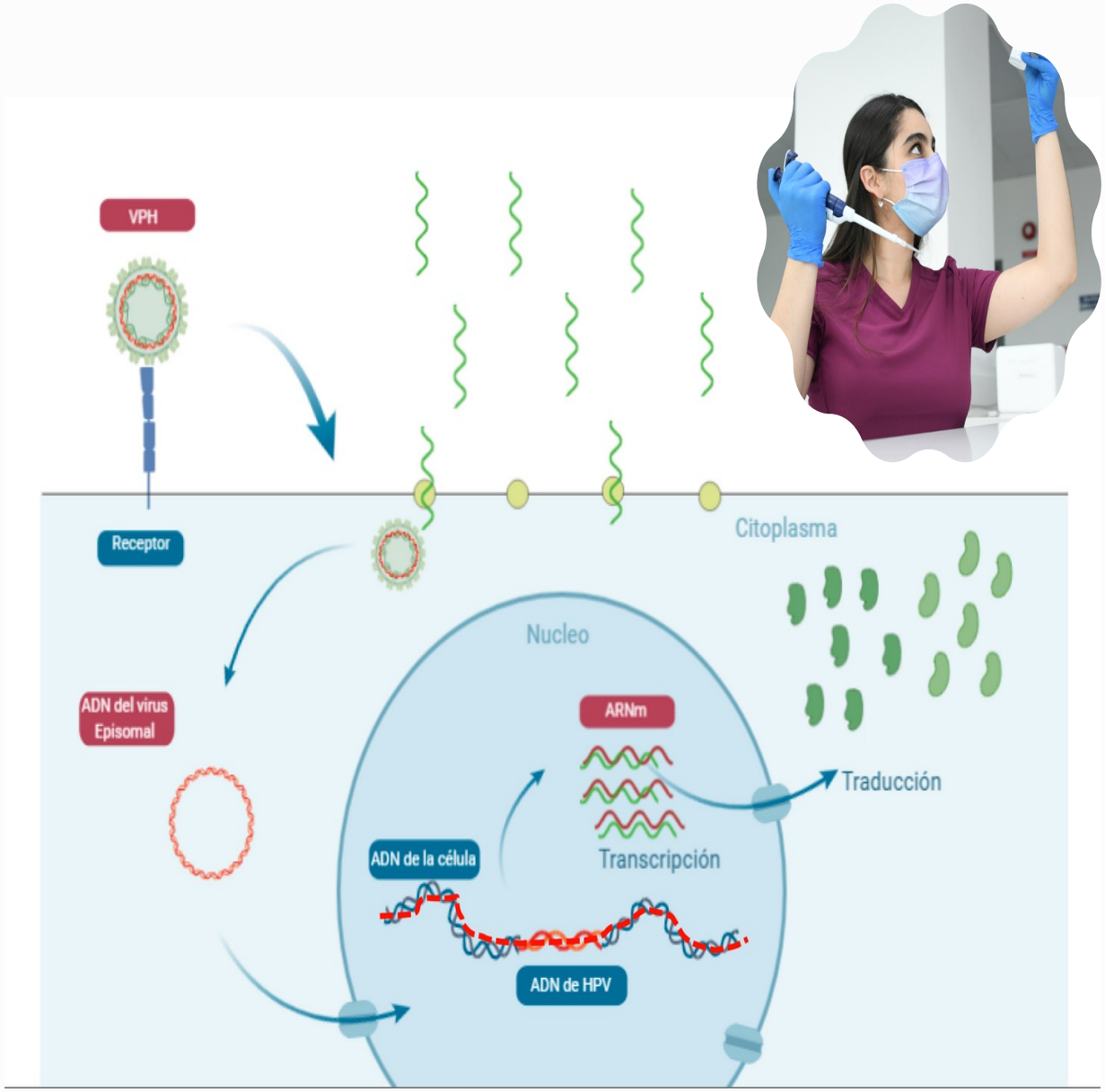
What can we do?

mRNA quantification

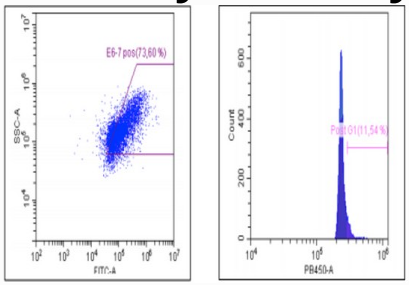


- Identifies high risk HPV (diagnosis and follow-up)
- High sensitivity and specificity with high predictive value (no unnecessary alerts)
- Well-known sample collection

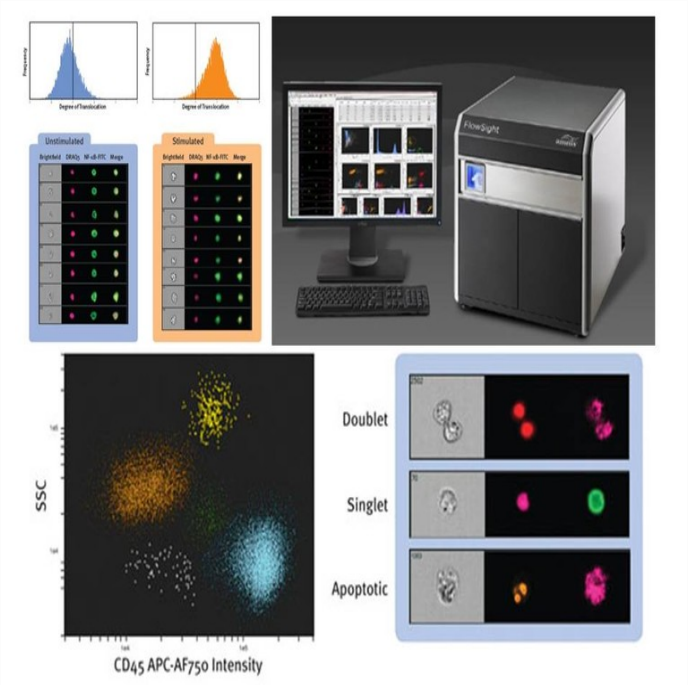
Unique oportunity at CICICA

Patients samples

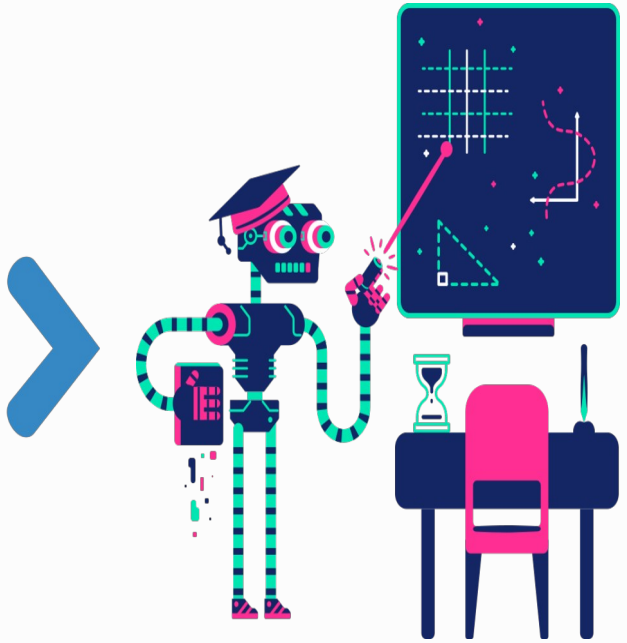
Flow cytometry



Validated test



Data analysis



Automation and Machine Learning

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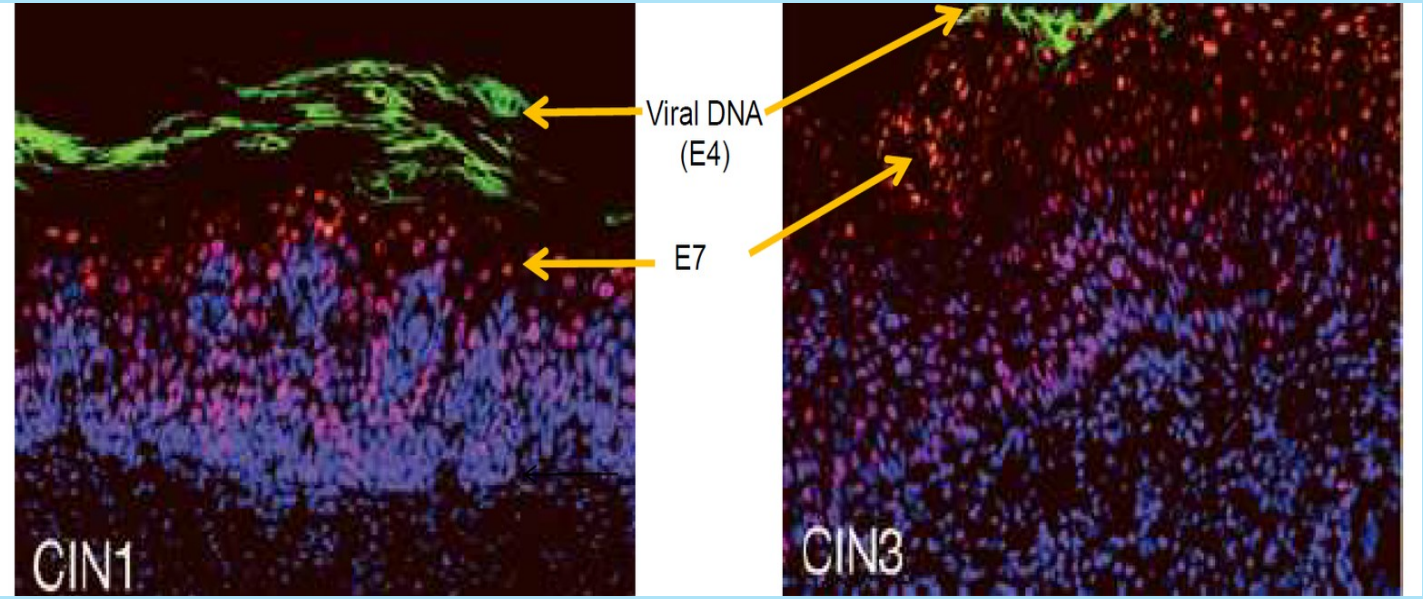
Our solution

for a secondary triage

Implementation of a test for malignant transformation in CR

The answer could be in the biology of the virus in order to distinguish between infection and transformation



DOI:10.1042/CS20050369

Observation of flow cytometry on images includes mRNA signals

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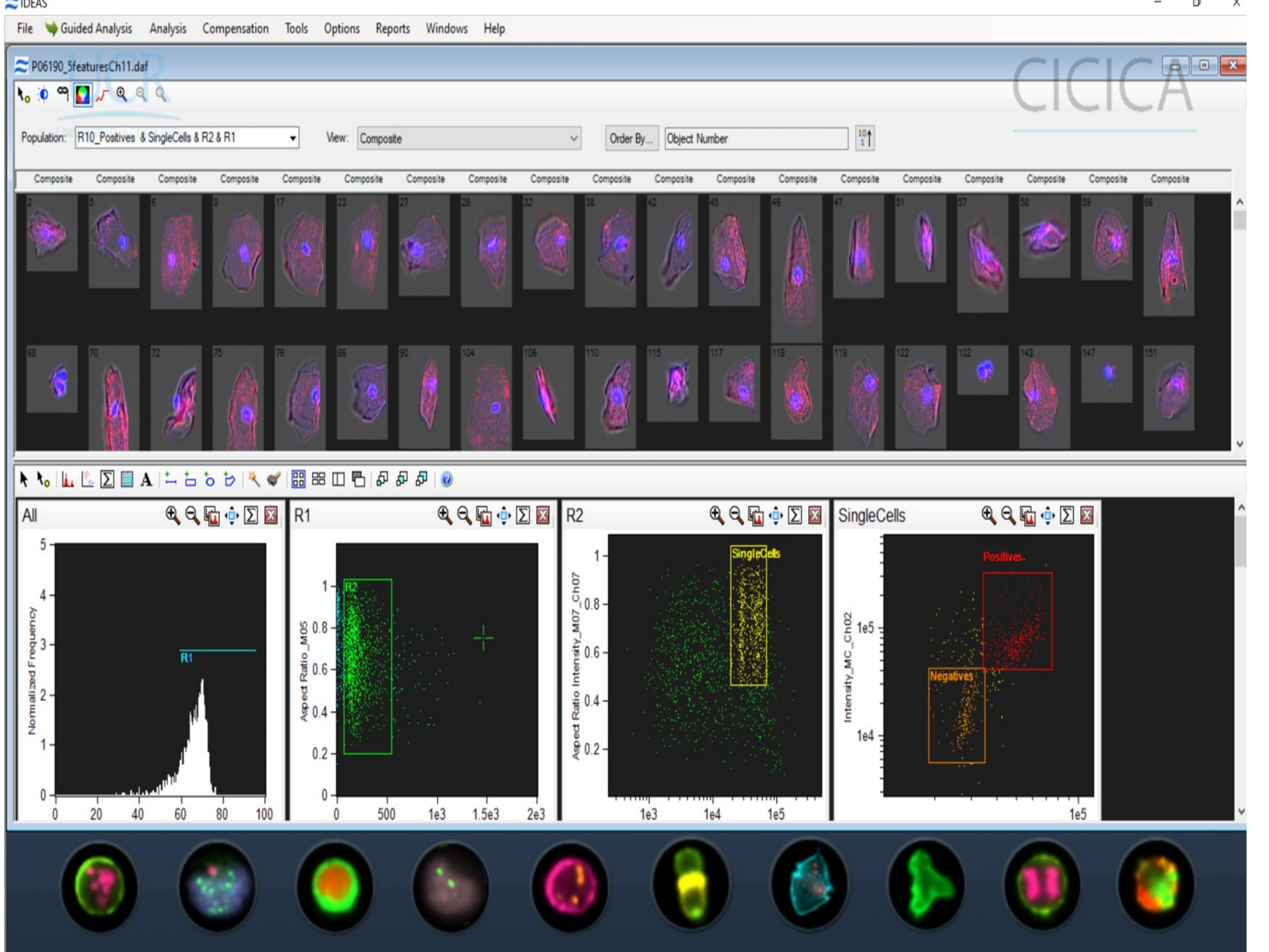
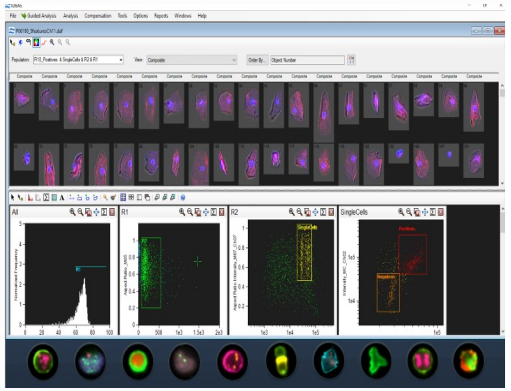
What we

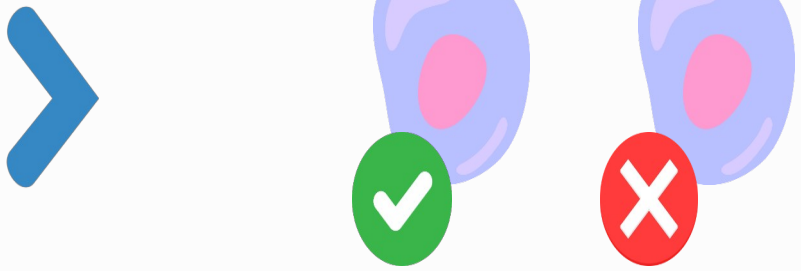
can obtain


IDEAS
File
Guided Analysis
Analysis
Compensation
Tools
Options
Reports
Windows
Help
P06190_5featuresCh11.daf
CICICA
Population:
R10_Positives & SingleCells & R2 & R1
View:
Composite
Order By...
Object Number
All
R1
R2
SingleCells
Normalized Frequency
Aspect Ratio_M05
Aspect Ratio Intensity_M07_Ch07
Intensity_MC_Ch02
Positives
Negatives

How does classification work?

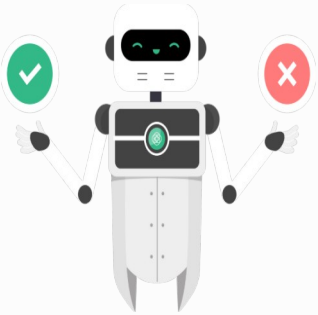


Flow cytometry images



Multiple examples of labeled cells

Disease pattern recognition



Pattern recognition algorithms

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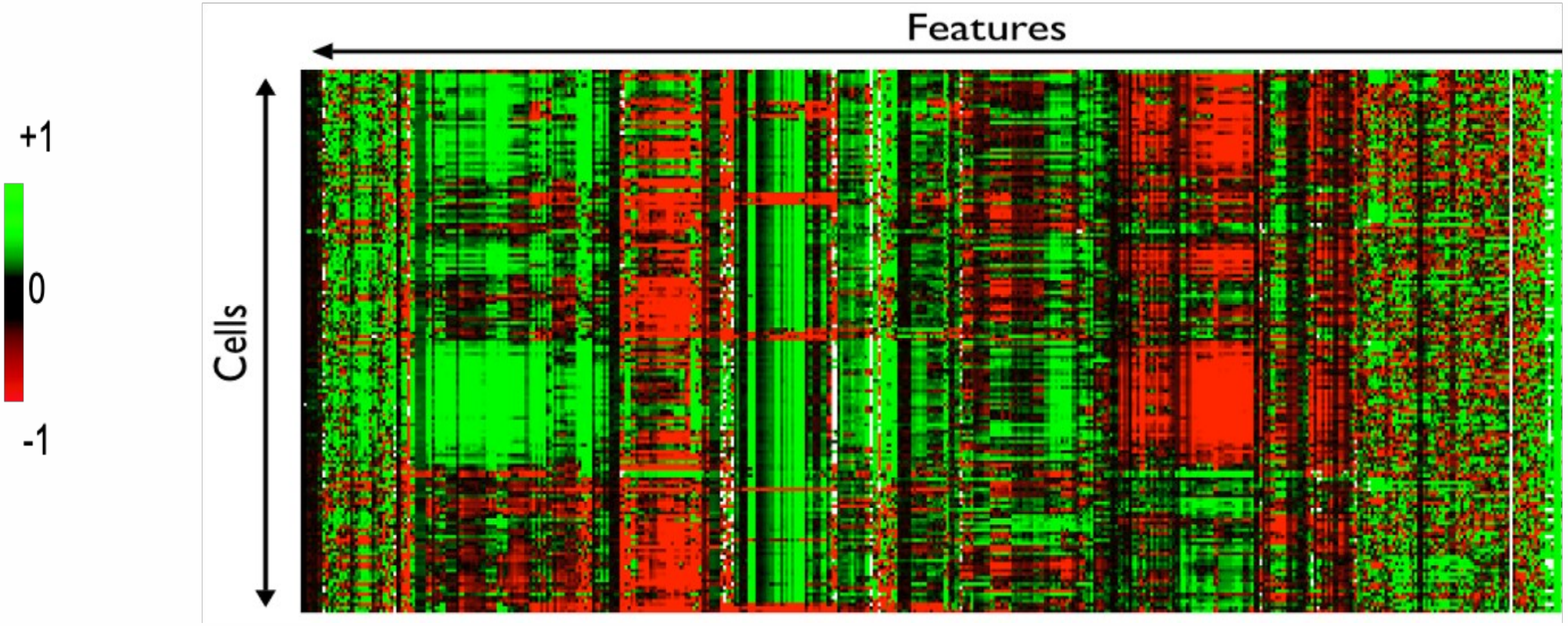
Images of single cells

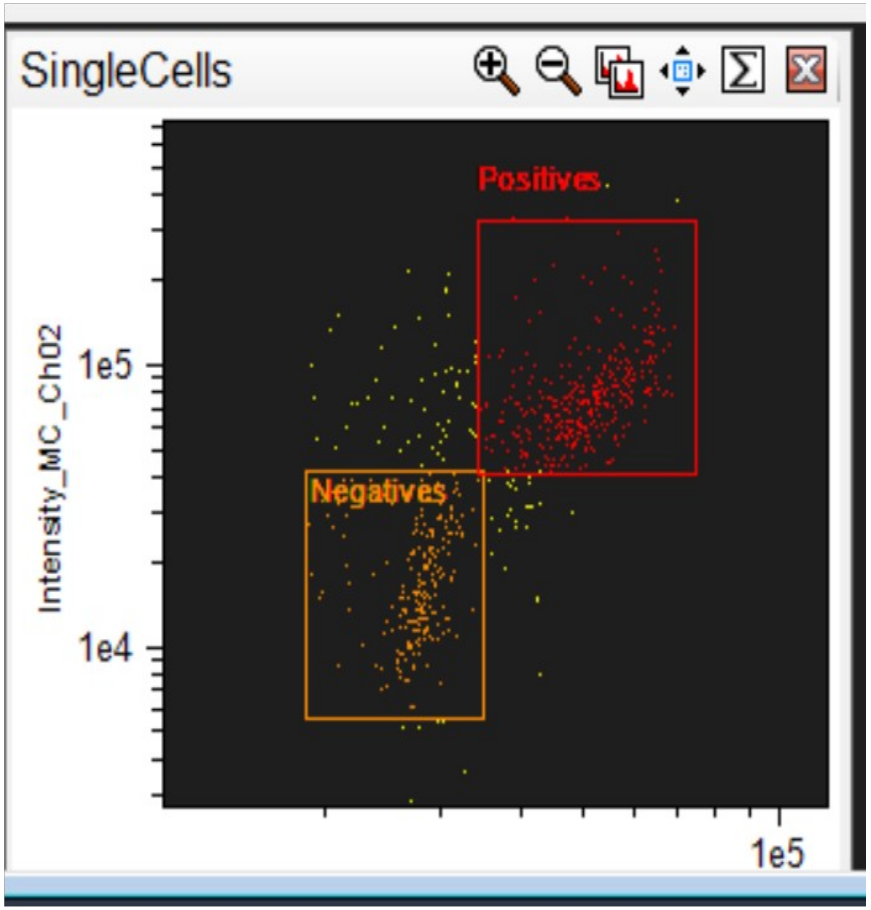
have lots of features

for classifiers



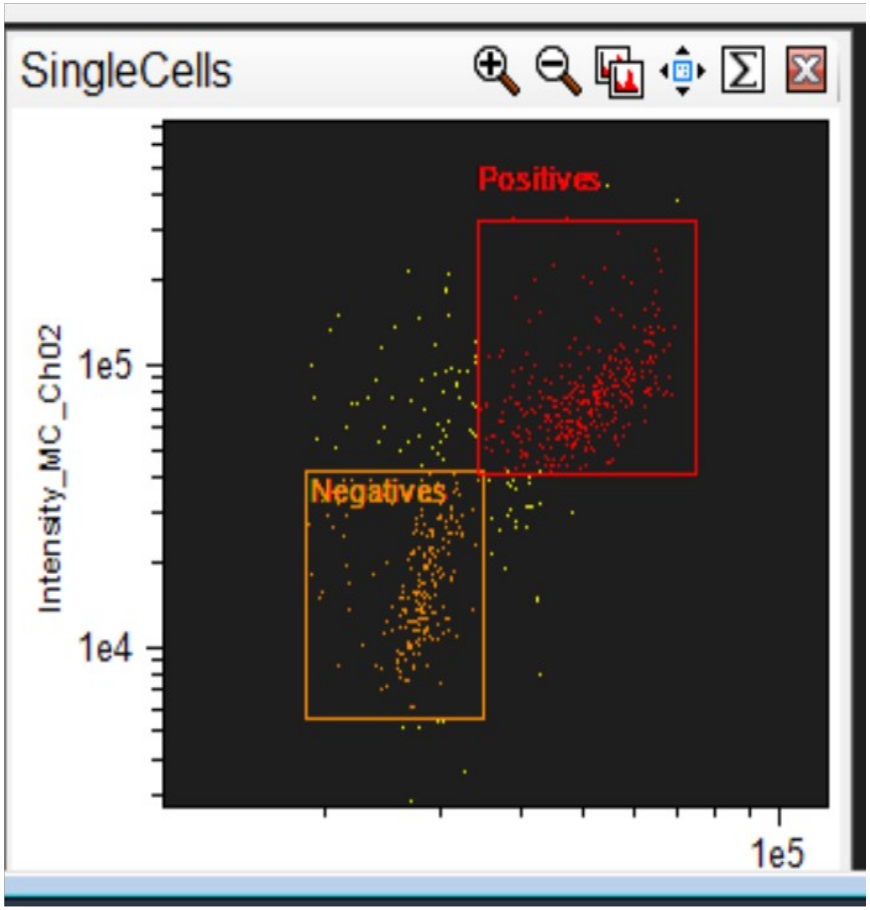
Data from images of individual cells allow classification

- For the first time, a lab has annotations of individual cells from clinical samples.
- Supervised learning from information of texture/morphology from other channels of fluorescence/bright field .



Data from images of individual cells allow classification

- Positive examples vs negative examples from the same clinical sample
- Feature ranking
- Building of a classifier independent from proba labeling.
- Very low cost of basic stainings!!



Research Center on Surgery and Cancer

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5% of World's biodiversity in 51100 Km^2

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