Personalized Analysis of Cancer Data: From Genes to Pathways

Eytan Domany
Dept of Physics of Complex Systems
Weizmann Institute of Science, Rehovot, Israel

Yotam Drier  Michal Sheffer  Anna Livshits  Gari Fuks
Carlos Caldas  Anna Git

Montpellier June 2017
Personalized Analysis of Cancer Data: From Genes to Pathways (and Back)

Eytan Domany
Dept of Physics of Complex Systems
Weizmann Institute of Science, Rehovot, Israel

Yotam Drier Michal Sheffer Anna Livshits Gari Fuks
Carlos Caldas Anna Git

Montpellier June 2017
BREAST CANCER: THE CHALLENGE:

PERSONALIZED PROGNOSTIC PREDICTIVE MEDICINE –

FOR BETTER TREATMENT OF CANCER

MEASURE (IN SAMPLE FROM TUMOR) GENOME-WIDE HIGH-THROUGHPUT DATA (MUTATIONS, EXPRESSION, METHYLATION, SNP, DNA COPY NUMBER, ETC), AND USE FOR

1. PROGNOSIS (PREDICT OUTCOME, AGGRESSIVENESS)

2. PREDICT RESPONSE TO THERAPY

OF INDIVIDUAL PATIENTS/TUMORS

BREAST CANCER - THE MAIN QUESTIONS:
1. CHEMOTHERAPY – YES/NO? 2. IF YES – WHICH?
SEARCH FOR “OMIC” MOLECULAR SIGNATURES SINCE THE CLASSICAL CLINICAL CRITERIA (NIH, ST. GALLEN, NPI) LEAD TO OVERTREATMENT
BREAST CANCER

DEATH RATE: 25/100,000 per year

INCIDENCE: ABOUT 1 OUT OF 9 WOMEN AFFECTED.

EARLY DISCOVERY: SMALL TUMOR ( < 2cm ), HAS NOT SPREAD TO LYMPH NODES, LOWEST GRADE, STAGE

GRADES 1, 2, 3
BREAST CANCER

DEATH RATE: 25/100,000 per year

INCIDENCE: ABOUT 1 OUT OF 9 WOMEN AFFECTED.

EARLY DISCOVERY: SMALL TUMOR (< 2cm), HAS NOT SPREAD TO LYMPH NODES, LOWEST GRADE, STAGE

TREATMENT: SURGICAL REMOVAL OF TUMOR + RADIOTHERAPY + HORMONAL THERAPY IF ER+; Herceptin if HER2+

STAGES OF BREAST CANCER

STAGE 0: Carcinoma In Situ (CIS) ductal CIS lobular CIS

STAGE I: spread to lymph nodes

STAGE I or II: duct cancer invading outside duct

STAGE III: spread to lymph nodes

GRADES 1, 2, 3
BREAST CANCER

DEATH RATE: 25/100,000 per year

INCIDENCE: ABOUT 1 OUT OF 9 WOMEN AFFECTED.

EARLY DISCOVERY: SMALL TUMOR (< 2cm), HAS NOT SPREAD TO LYMPH NODES, LOWEST GRADE, STAGE

TREATMENT: SURGICAL REMOVAL OF TUMOR + RADIOTHERAPY + HORMONAL THERAPY IF ER+; Herceptin if HER2+

CHEMOTHERAPY ??? No CHEMO if Low Risk

DECISION Yes/No was TAKEN ON THE BASIS OF CLINICAL PARAMETERS: NIH, St Gallen, NPI CRITERIA

STAGES OF BREAST CANCER
Stage III: spread to lymph nodes
Stage I or II: duct cancer invading outside duct
Stage 0: Carcinoma In Situ [CIS] lobular CIS ductal CIS

Normal cells Abnormal cell Abnormal cells Tumor

GRADES 1, 2, 3
BREAST CANCER

DEATH RATE 25/100,000 per year

INCIDENCE: ABOUT 1 OUT OF 9 WOMEN AFFECTED.

EARLY DISCOVERY: SMALL TUMOR ( < 2cm ), HAS NOT SPREAD TO LYMPH NODES, LOWEST GRADE, STAGE

TREATMENT: SURGICAL REMOVAL OF TUMOR + RADIOTHERAPY + HORMONAL THERAPY IF ER+; Herceptin if HER2+

CHEMOTHERAPY ??? No CHEMO if Low Risk

DECISION Yes/No was TAKEN ON THE BASIS OF CLINICAL PARAMETERS: NIH, St Gallen, NPI CRITERIA

=> SEVERE OVERTREATMENT

STAGES OF BREAST CANCER

Stage 0: Carcinoma In Situ [CIS] ductal CIS lobular CIS

Stage I: spread to lymph nodes

Stage I or II: duct cancer invading outside duct

STAGES OF BREAST CANCER

Normal cells Abnormal cell Abnormal cells Tumor

GRADES 1,2,3
A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER:

A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

<table>
<thead>
<tr>
<th>Wang et al.</th>
<th>Van’t Veer. et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>List = 76 genes</td>
<td>List = 70 genes</td>
</tr>
<tr>
<td>(Rotterdam</td>
<td>(Amsterdam</td>
</tr>
<tr>
<td>Signature)</td>
<td>signature)</td>
</tr>
</tbody>
</table>
A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)

A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)


Different Platforms!
Different Populations of Patients!
Different Types of Analysis!
A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)


76 3 70

Different Platforms! Different Populations of Patients! Different Types of Analysis! NO!!

A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)


INHERENT LACK OF ROBUSTNESS OF PROGNOSTIC GENE LISTS* (GENES WERE RANKED BY CORRELATION OF EXPRESSION WITH OUTCOME – TOP 70 MADE THE LIST)

PROGNOSTIC PERFORMANCE OF THE 70 TOP-RANKED GENES

Van’t Veer

PROGNOSTIC PERFORMANCE OF OTHER GROUPS OF 70 GENES

Van’t Veer

PROGNOSTIC PERFORMANCE OF OTHER GROUPS OF 70 GENES

THE PROGNOSTIC VALUE OF THE SELECTED 70 GENES IS SIMILAR TO THAT OF MOST OTHER RANDOM SETS OF 70 GENES

A SUCCESSFUL GENE EXPRESSION BASED PROGNOSTIC SIGNATURE FOR EARLY-DISCOVERY BREAST CANCER: ANOTHER ONE:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)


INHERENT LACK OF ROBUSTNESS OF RANKED GENE LISTS*
HOW MANY SAMPLES ARE NEEDED TO GET A ROBUST LIST OF 70?**
(ROBUST = 50% OVERLAP, $f = 0.50$) => PHYSICS!!!

*Ein Dor et al Bioinformatics 2005, **PNAS 2006;
\[ P_{n,\alpha}(f) = \frac{1}{N_{r}} \int_{0}^{\infty} dx_{1} dx_{2} \sum_{h,l \in \{0,1\}^{N_{g}}} \left( \delta \left[ \sum_{j=1}^{N_{g}} h_{j} - N_{\text{TOP}} \right] \delta \left[ \sum_{j=1}^{N_{g}} l_{j} - N_{\text{TOP}} \right] \delta \left[ \sum_{j=1}^{N_{g}} h_{j} l_{j} - f N_{\text{TOP}} \right] \right) \]

\[ N_{\text{TOP}} = \alpha N_{g} \ (=70) \ [N_{g} = \#\text{genes}, \ n = \#\text{samples}] \]

\[ P(f) \] \text{ is given as a sum over } 2^{N_{g}} \text{ binary variables, coupled by 3 constraints; use saddle point integration, large } N_{g} \text{ expansion to get:}

\[ P_{n,\alpha}(f) = \frac{1}{\sqrt{2\pi} \sum_{n}(\alpha)} e^{\frac{(f-f_{n}^{*}(\alpha))^{2}}{2(\sum_{n}(\alpha))^{2}}} \]

\[ f_{n}^{*}(\alpha) \quad \text{– Typical Overlap} \]

\[ \sum_{n}(\alpha) \quad \text{– St.D. of the distribution} \]
Van’t Veer needs 2200 training samples to get 50% typical overlap between two lists of top 70 genes (ranked by correlation with outcome).

Ein-Dor et al PNAS 2006

\[ f_n^* = 0.5 \text{ (typical } f \text{) ??} \]
A successful gene expression based prognostic signature for early-discovery breast cancer: another one:

Wang et al. Lancet 2005, List = 76 genes (Rotterdam Signature)


INHERENT LACK OF ROBUSTNESS OF RANKED GENE LISTS*

HOW MANY SAMPLES ARE NEEDED TO GET A ROBUST LIST OF 70?**

NO IMPROVEMENT OVER “CLASSICAL” METHODS (DESPITE CLAIMS)

(BUT - SEE Cardoso NEJM 2016)

NO BIOLOGICAL INSIGHT GAINED

*Ein Dor et al Bioinformatics 2005, **PNAS 2006; Drier PLoS ONE 2011
CURRENTLY USED (TRANSCRIPT **OMIC**) PREDICTORS:

<table>
<thead>
<tr>
<th># GENES</th>
<th>PLATFORM</th>
<th>SAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammaprint + Classical (Adjuvant!)</td>
<td>70</td>
<td>Microarray</td>
</tr>
<tr>
<td>Oncotype Dx  (<strong>Knowledge –based</strong>)</td>
<td>21</td>
<td>qRT-PCR</td>
</tr>
<tr>
<td>Prosigna (PAM 50)</td>
<td>50</td>
<td>Nanostring</td>
</tr>
</tbody>
</table>

LIMITED SUCCESS, DID NOT REPLACE CLASSICAL CLINICAL VARIABLES
FAILURES - WHY?:

SOME OF THE REASONS (1. CULTURAL AND 2. TECHNICAL):

1. THE FIELD WAS DOMINATED BY TWO EXTREMES:
   a. USE **NO** BIOLOGICAL/CLINICAL EXISTING KNOWLEDGE,
      (turn ignorance into a virtue)
   
   or

   b. DEMAND/ASSUME FULL DETAILED MECHANISTIC KNOWLEDGE
      (don’t dare talk to me unless you know and use all details)

2. FEW POINTS (TUMORS, 100 - 1000) IN HIGH DIMENSIONAL
   SPACES (GENES: 1000 – 10,000): “CURSE OF DIMENSIONALITY”

   SINGLE-GENE BASED DESCRIPTION = “ATOMISTIC” APPROACH
WHAT’S WRONG WITH THIS CAR?:

“ATOMISTIC” APPROACH:

MEASURE SOME PROPERTY (e.g. TEMPERATURE) OF EVERY SINGLE COMPONENT – 12,000 NUMBERS CHARACTERIZE THE “STATE “ OF EACH CAR

TRY TO DETERMINE THE FEATURES THAT CAN BE USED TO TELL HEALTHY CARS FROM SICK ONES.

NO EXISTING KNOWLEDGE ABOUT CARS IS USED
A “PHENOMENOLOGICAL” “SYSTEMS” APPROACH

MEASURE FOR EACH SYSTEM ONE NUMBER, THAT INDICATES THE DEVIATION OF THIS SYSTEM’S FUNCTIONING FROM NORMAL.

EACH CAR IS CHARACTERIZED BY A SET OF SUCH “SYSTEM-LEVEL INDICATORS” (ABOUT 100) - USE THESE TO SEPARATE HEALTHY FROM SICK CARS
PATHWAY (OR - BIOLOGICAL PROCESS) – BASED ANALYSIS: THE IDEA

a. USE EXPRESSION (OR ANY OTHER) HIGH-THROUGHPUT DATA FROM A LARGE NUMBER OF SAMPLES.

Drier, Sheffer & Domany *PNAS 2013*
a. USE EXPRESSION DATA


3. BREAST CANCER: METABRIC Curtis et al Nature 2012: 1000+1000 TUMORS, 144 NORMAL TCGA, 988 TUMORS, 106 NORMAL

4. THYROID CANCER: TCGA PROJECT, ON 58 NORMAL, 482 CANCER

5. KIDNEY CANCER, TCGA, 870 TUMOR, 120 NORMAL
PATHWAY (OR - BIOLOGICAL PROCESS) – BASED ANALYSIS: THE IDEA

a. USE EXPRESSION (OR ANY OTHER) HIGH-THROUGHPUT DATA FROM A LARGE NUMBER OF SAMPLES.

b. USE BIOLOGICAL KNOWLEDGE – LISTS OF (10 - 100) GENES THAT BELONG TO A BIOLOGICAL PROCESS OR PATHWAY
b. USE EXISTING KNOWLEDGE - ASSIGNMENT OF GENES TO PATHWAYS $P$

USE KEGG, BioCarta FROM MSigDB, AND NCI-Nature Pathway Interaction DATABASES

Histogram of sizes of final gene sets used

Number of pathways

Number of genes in pathway

Reactome
BioCarta
b. USE EXISTING KNOWLEDGE - ASSIGNMENT OF GENES TO PATHWAYS $P$

USE KEGG, BioCarta FROM MSigDB, AND NCI-Nature Pathway Interaction DATABASES

TYPICALLY – TENS OF GENES IN A PATHWAY; HUNDREDS OF SAMPLES
“CURSE OF DIMENSIONALITY” IS ELIMINATED
TYPICALLY – FEW HUNDRED GENE SETS PASS FILTERS
PATHWAY (OR - BIOLOGICAL PROCESS) – BASED ANALYSIS: THE IDEA

a. USE EXPRESSION (OR ANY OTHER) HIGH-THROUGHPUT DATA FROM A LARGE NUMBER OF SAMPLES.

b. USE BIOLOGICAL KNOWLEDGE – LISTS OF (10 - 100) GENES THAT BELONG TO A BIOLOGICAL PROCESS OR PATHWAY $P$

c. DERIVE FOR EACH SAMPLE $i$ AND PATHWAY $P$ A “PATHWAY Deregulation Score” $D(i,P)$

Drier, Sheffer & Domany PNAS 2013
c. FOR EACH SAMPLE \( i \) AND PATHWAY \( P \) - CALCULATING THE PATHWAY DEREGLULATION SCORE (PDS)

1. Consider pathway \( P \); identify \( d_P \) genes that belong to it. Sample \( i \) is represented by a point \( X_i \) in the space of the expression values of these genes.

KEGG APOPTOSIS PATHWAY, \( d_P = 33 \) GENES, COLON DATA
c. PATHWAY DEREGULATION SCORE (PDS)

2. Calculate the *Principal Curve* (*Hastie & Stuezle 1989*) of the cloud of points formed by the full sample set.
c. PATHWAY DEREGULATION SCORE (PDS)

3. Project every sample onto the principal curve; projection of sample $i$ is $Y_i$. The projection to the extremal point near the Normal samples is the Reference Point $N$. 

![Diagram showing the projection of samples onto principal components](image)
c. PATHWAY DEREGULATION SCORE (PDS)

4. The distance of $Y_i$ from $N$, measured along the principal curve, is $D_i(P)$, the Deregulation Score of pathway $P$ in sample $i$. 
PATHWAY (OR - BIOLOGICAL PROCESS) – BASED ANALYSIS: 
THE IDEA

a. USE EXPRESSION (OR ANY OTHER) HIGH-THROUGHPUT DATA FROM A LARGE NUMBER OF SAMPLES.

b. USE BIOLOGICAL KNOWLEDGE – LISTS OF (10 - 100) GENES THAT BELONG TO A BIOLOGICAL PROCESS OR PATHWAY $P$

c. DERIVE FOR EACH SAMPLE $i$ AND PATHWAY $P$ A “PATHWAY DEREGULATION SCORE” $D(i,P)$

d. DO THIS FOR $N_P \sim$ FEW HUNDRED PATHWAYS

e. A SAMPLE IS REPRESENTED IN TERMS OF ITS $N_P$ PATHWAY DEREGULATION SCORES => DESCRIBED BY $N_P$ PARAMETERS

f. PERFORM ALL ANALYSIS USING THESE “SYSTEM-LEVEL” VARIABLES WITH CLEAR BIOLOGICAL MEANING.

Drier, Sheffer & Domany *PNAS* 2013
Using expression data from 1992 TUMOR and 144 NORMAL samples
(997 in “Discovery set”, 995 in “Validation”)

Calculate (using “Pathifier” analysis*) a Pathway Deregulation Score (PDS)
for 552 pathways/biological processes, for each sample (Discovery + Normal)

\[ D(P,i) = \text{PDS of pathway } P \text{ in sample } i \] – represent the extent to which pathway 
\( P \) is deregulated in sample \( i \)

*Drier, Sheffer & Domany PNAS 2013
PDS OF 552 PATHWAYS: EACH SAMPLE (144 NORMAL, 997 BREAST TUMOR) IS REPRESENTED BY 552 SUCH PATHWAY–BASED SCORES

Livshitz et al Oncotarget 2015
PERFORM ANALYSIS IN THIS SPACE: REORDERING* SAMPLES (AND PATHWAYS) REVEALS STRUCTURE IN DATA**

*Tsafir et al *Bioinformatics* (2005)

PERFORM ANALYSIS IN THIS SPACE: REORDERING* SAMPLES (AND PATHWAYS) REVEALS STRUCTURE IN DATA**

*Tsafrir et al *Bioinformatics* (2005)

PERFORM ANALYSIS IN THIS SPACE: REORDERING SAMPLES (AND PATHWAYS) REVEALS STRUCTURE IN DATA
552 by 1141 PDS-MATRIX CAPTURES KNOWN SUBTYPES
APPLY METHOD TO BREAST CANCER:
FOCUS ON TWO GROUPS OF BASAL / TRIPLE NEGATIVE TUMORS

BASAL/TN SUBTYPE – HIGH AND LOW IMMUNE INVOLVEMENT

DIFFERENT OUTCOME/SURVIVAL FOR THE TWO GROUPS!
CLINICAL SIGNIFICANCE: FOR BASAL / TN SUBTYPE, HIGH IMMUNE INVOLVEMENT ➔ BETTER SURVIVAL

Survival rate

\[ p = 0.013 \]

CLINICAL SIGNIFICANCE:
Basal tumors with HIGH IMMUNE system involvement – better survival
Basal tumors with LOW IMMUNE system involvement -- worse
CLINICAL SIGNIFICANCE:
Basal tumors with HIGH IMMUNE system involvement – better survival
Basal tumors with LOW IMMUNE system involvement -- worse

BIOLOGICAL INTERPRETATION:
HIGH IMMUNE INVOLVEMENT (PDS) ⇔ HIGH TIL LEVEL

BIOLOGICAL INTERPRETATION:
HIGH IMMUNE PDS ⇔ high level of Tumor Infiltrating Lymphocytes

Highest correlation with TIL levels
- for T-CELL related PATHWAYS
- cell-specific signatures ⇒ Tcells
⇒ BIOMARKER!

Survival rate

\[ p=0.013 \]
CLINICAL SIGNIFICANCE:
Basal tumors with HIGH IMMUNE system involvement – better survival
Basal tumors with LOW IMMUNE system involvement -- worse

BIOLOGICAL INTERPRETATION:
HIGH IMMUNE INVOLVEMENT (PDS) ↔ HIGH TIL LEVEL

Highest correlation with TIL levels
- for T-CELL related PATHWAYS
- cell-specific signatures => Tcells

PROGNOSTIC BIOMARKER?
Alexe et al (2007): no difference in survival between TN tumors with high/low immune involvement
PREDICTIVE BIOMARKER: FOR BASAL/TN SUBTYPE, IMMUNE INVOLVEMENT ➔ BETTER RESPONSE TO THERAPY

Alexe et al (2007): TN PATIENTS DID NOT RECEIVE CHEMOTHERAPY


IS THE DIFFERENCE IN OUTCOME DUE TO TREATMENT?

p = 0.013
PREDICTIVE BIOMARKER: FOR BASAL/TN SUBTYPE, IMMUNE INVOLVEMENT ➔ BETTER RESPONSE TO THERAPY

Alexe et al (2007): TN PATIENTS DID NOT RECEIVE CHEMOTHERAPY
IS THE DIFFERENCE IN OUTCOME DUE TO TREATMENT?

- ALL BASAL PATIENTS: $p=0.013$
- BASAL PATIENTS-TREATED: $p=0.006$
- BASAL PATIENTS-UNTREATED: $p=0.66$
**PREDICTIVE BIOMARKER:** FOR BASAL/TN SUBTYPE, IMMUNE INVOLVEMENT ➔ BETTER RESPONSE TO THERAPY

Alexe et al (2007): TN PATIENTS DID NOT RECEIVE CHEMOTHERAPY


IS THE DIFFERENCE IN OUTCOME DUE TO TREATMENT?

DIFFERENCE IN SURVIVAL BETWEEN BASAL PATIENTS WITH HIGH vs LOW IMMUNE INVOLVEMENT IS OBSERVED ONLY FOR PATIENTS WHO RECEIVED CHEMOTHERAPY. PREDICTIVE BIOMARKER?
PREDICTIVE BIOMARKER: FOR BASAL SUBTYPES, IMMUNE INVOLVEMENT ➔ BETTER RESPONSE TO THERAPY

Possible interpretation 1: Anthracyclins are killing basal patients with low immune involvement, and have no effect on patients with high immune involvement. SHOCKING!!
PREDICTIVE BIOMARKER: FOR BASAL SUBTYPES, IMMUNE INVOLVEMENT ➔ BETTER RESPONSE TO THERAPY

Interpretation 2: High risk patients (bad indicators) were sent to chemo. If low immune — chemo did not help. High immune — chemo did help!

Possible Interpretation 1: Anthracyclins are killing basal patients with low immune involvement, and have no effect on patients with high immune involvement. Shocking!!
PREDICTIVE BIOMARKER: FOR BASAL SUBTYPES, IMMUNE INVOLVEMENT ➤ BETTER RESPONSE TO THERAPY

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>No CT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 7</td>
<td>46</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>(Low Imm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster 8</td>
<td>36</td>
<td>29</td>
<td>65</td>
</tr>
<tr>
<td>(High Imm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>45</td>
<td>127</td>
</tr>
</tbody>
</table>

WE USED CT/NO CT AS A PROXY FOR (CLASSICAL) HIGH/LOW RISK. HIGH IMMUNE INVOLVEMENT/TIL INDICATES GOOD RESPONSE OF HIGH-RISK BASAL/TN PATIENTS TO ANTHRACYCLINS. DO NOT TREAT (WITH ANTHRACYCLINS) HIGH RISK BASAL/TN PATIENTS WITH LOW TIL. PREDICTIVE BIOMARKER!

Anthracyclins & immune system:
Zitvogel Cell Death & Differ. (2014)
Nat. Med. (2014)
Oncoimmunology (2014)
SUGGESTED DECISION PIPELINE:

1. IDENTIFY TRIPLE NEGATIVE PATIENTS (HISTOCHEMISTRY)

2. USE CLINICAL (OR OTHER) INDICATORS TO IDENTIFY HIGH RISK PATIENTS, CANDIDATES FOR CHEMOTHERAPY

3. FOR HIGH-RISK PATIENTS:
   MEASURE T – CELL INFILTRATE LEVEL IN TUMOR,
   or OTHER (SINGLE-GENE BASED) BIOMARKER. CANDIDATES: SYK, CD14, CXCR3, CXCL9

4. IF HIGH TIL – DO NOT TREAT WITH ANTHRACYCLINES*

*Livshits et al Oncotarget (2015)*
TAKE – HOME LESSONS*:

1. DO NOT USE IGNORANCE-BASED “TOP RANKED” SINGLE GENE LISTS: THEY ARE UNSTABLE**, MOSTLY DEVOID OF BIOLOGICAL MEANING***.

2. CHARACTERIZE TUMORS BY KNOWLEDGE-BASED, SYSTEM-LEVEL VARIABLES# (Pathway Deregulation Scores).

3. LOWER AIMS: NO SILVER BULLET THAT WORKS FOR ALL BREAST CANCER SUBTYPES AND ALL CHEMOTHERAPIES.

4. GENOMIC BIOMARKERS SHOULD COMPLEMENT CLASSICAL CLINICAL RISK INDICATORS (NOT REPLACE THEM).

* Domany Cancer Res (2014)
** Ein-Dor et al Bioinformatics (2005); PNAS (2006)
Michiels et al Lancet (2005)
*** Drier et al PLoS ONE (2011)
# Drier et al PNAS (2013); Shi et al Annals Onc (2016)
SUPPORT (CURRENT AND PAST)

The Leir Charitable Foundation

German-Israeli cooperation Project (DIP)

Israel Ministry of Science (IMoS)

Israel Ministry of Industry and Commerce/NOFAR

Israel Science Foundation (ISF)

National Cancer Institute – NIH Program Project Grant

EC Research Grants

Minerva, Wolfson, Mario Negri Foundations
THANKS FOR LISTENING

&

APOLOGIES FOR RUNNING OVER TIME