CANCER OF UNKNOWN PRIMARY: A Diagnostic and Therapeutic Dilemma

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ESO Coordinator on Career Development Programme

Split, ESO-ESMO MCO, April 2019
What is the incidence of cancer of unknown primary site?
INCIDENCE AND MORTALITY OF CUP

• CUP accounts for 3-5% of all human cancers

• It is considered to be the 8th most frequent malignant tumor

• In Europe the incidence decreased from 14 per 100,000 person in 2000 to 7.0 in 2012 (EJC 101:77-86, 2018)

• In USA the incidence decreased since 1980’s by 3.6% per year (Cancer Causes Control 25:747-757, 2014)
WHAT ARE THE INTERPRETATIONS?

- Improved diagnostics (immunohistochemistry, molecular gene expression profiling and imaging technology) have improved the ability to detect the primary site.

- Better smoking control in US.
RISK FACTORS

- Risks of being diagnosed with CUP was strongly related to smoking.

  - i) Current smokers (relative risk: 3.66) and
  - ii) Heavy smokers (26+ cigarette/d) (relative risk: 5.12) died within 12 months

Int J Cancer 135: 2475, 2014
CLINICAL PRESENTATION OF CUP
THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE

FUNDAMENTAL CHARACTERISTICS
FUNDAMENTAL CHARACTERISTICS

- Early dissemination
- Clinical absence of primary at presentation
- Aggressiveness
- Unpredictable metastatic pattern
Cancer of Unknown Primary Site:

One or more Diseases?
### HISTOLOGICAL CLASSIFICATION

<table>
<thead>
<tr>
<th>Histology</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>50 %</td>
</tr>
<tr>
<td>Well to moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>35 %</td>
</tr>
<tr>
<td><strong>Squamous cell carcinoma</strong></td>
<td>10 %</td>
</tr>
<tr>
<td><strong>Undifferentiated neoplasms</strong></td>
<td>5 %</td>
</tr>
<tr>
<td>Not specified carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
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<tr>
<td>Germ cell tumors</td>
<td></td>
</tr>
<tr>
<td>Melanomas</td>
<td></td>
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<tr>
<td>Sarcomas</td>
<td></td>
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<tr>
<td>Embryonal malignancies</td>
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</tbody>
</table>
CLINICOPATHOLOGICAL ENTITIES OF CUP

**ORGAN**

*Liver* (mainly) and/or other organs

*Lymph nodes*

  Mediastinal – Retroperitoneal (midline distribution)

  **HISTOLOGY**

  AdenoCa M or P diff

  U or P diff Ca

  AdenoCa W to P diff

  SCC Ca

  U Ca, SCC, mixed SCC / adenoCa

\[W = \text{well}, \quad M = \text{moderately}, \quad P = \text{poorly}, \quad U = \text{undifferentiated}\]
**Peritoneal cavity**

Peritoneal adenocarcinomatosis in females

Malignant ascites of other unknown origin

**Lungs**

Pulmonary metastases

Pleural effusion

Papillary or serous adenocarcinoma

Mucin adenocarcinoma M or P diff

Adenocarcinoma various diff

Adenocarcinoma M or P diff

*W = well,  M = moderately,  P = poorly,  U = undifferentiated*
**Bones**
(solitary or multiple) AdenoCa of various diff

**Brain**
(solitary of multiple) AdenoCa of various diff or squamous cell Ca

**Neuroendocrine tumors**
P diff Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca

**Melanoma**
U neoplasm with melanoma features.

\[W = \text{well}, \quad M = \text{moderately}, \quad P = \text{poorly}, \quad U = \text{undifferentiated}\]
WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR?
HOW DO WE SEARCH FOR THE PRIMARY?

By HISTOPATHOLOGY
- Immunohistochemistry
- Advanced Molecular Technology

By IMAGING
- Conventional Radiology
- Ultrasenography
- CT-scans
  - MRIs
- PET-scans
- Mammography

By ENDOSCOPY
- ENT panendoscopy
- Bronchoscopy
- Colonoscopy
- Proctoscopy
- Colposcopy
By
HISTOPATHOLOGY
And
IMMUNOCHEMISTRY
Cytokeratins (CKS)

Monoclonal antibodies against cytokeratin polypeptides CK7 and CK20
CK7  CK20

CK7 + CK20 +
- Urothelial tumors
- Ovarian mucinous adenocarcinoma
- Pancreatic adenocarcinoma
- Cholangiocarcinoma

CK7 + CK20 -
- Lung adenocarcinoma
- Breast carcinoma
- Thyroid carcinoma
- Endometrial carcinoma
- Cervical carcinoma
- Salivary gland carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma

CK7 - CK20 -
- Colorectal Carcinoma
- Merkel cell carcinoma

CK7 - CK20 -
- Hepatocellular carcinoma
- Renal cell carcinoma
- Prostate carcinoma
- Squamous cell & small cell lung carcinoma
- Head & neck carcinoma
MOLECULAR ANALYSIS
[Microarray Platforms]

> 80 - 90 % accuracy
# Gene expression profiling Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Platform</th>
<th>Tissue</th>
<th>No. of Tumor types</th>
<th>Number of genes</th>
<th>Accuracy in known tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veridex</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>6 and “other”</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>Pathwork Diagnostics</td>
<td>cDNA microarray</td>
<td>Frozen/FFPE</td>
<td>15</td>
<td>1500</td>
<td>89</td>
</tr>
<tr>
<td>Tissue of Origin test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosetta Genomics MiReview met</td>
<td>RT-PCR miRNA</td>
<td>FFPE</td>
<td>22</td>
<td>48 miRNAs</td>
<td>86</td>
</tr>
<tr>
<td>bioTheranostics CancerType ID</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>39 (including subtypes)</td>
<td>92</td>
<td>86</td>
</tr>
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</table>
LIQUID BIOPSY IN CUP

Liquid biopsy opens a new diagnostic, predictive and prognostic window in CUP that may lead to substantial improvement in the management of patients with CUP.

El Rassy, H Khaled, N Pavlidis, Eur J Cancer 105:28-32, 2018
**ENDOSCOPY**

- Should always be symptoms - or signs oriented investigational procedures

- **ENT panendoscopy**: in cervical node involvement
- **Bronchoscopy**: in radiographic indications or symptoms
- **Colonoscopy**: in relevant symptoms and signs
- **Proctoscopy**: in inguinal node involvement
- **Colposcopy**: in inguinal node involvement
# Imaging Studies in COP

<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Diagnostic Value</th>
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<tbody>
<tr>
<td>CT-scans</td>
<td>40% accuracy / Guidance to biopsy</td>
</tr>
<tr>
<td>MRI (breast)</td>
<td>60% accuracy</td>
</tr>
<tr>
<td>FDG-PET SCAN</td>
<td>43% accuracy / more sensitive for occult H+N (80-85%)</td>
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NCCN 2019: The exact role of PET/CT remains undefined because of the lack of large prospective clinical trials comparing PET/CT with conventional imaging modalities.
SERUM TUMOR MARKERS

- Routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance

- A non–specific multiple overexpression of the adenocarcinoma markers (CEA, CA 125, CA 15-3, CA 19-9) has been observed in the majority of CUP patients.

- Worthwhile to request:
  - PSA in men with bone metastatic adenocarcinoma
  - B-HCG & AFP in men with an undifferentiated tumor
  - AFP in patients with hepatic tumors
  - CA 125 women with papillary adenocarcinoma of peritoneal cavity.
  - CA 15-3 women with adenocarcinoma involving only axillary lymph nodes.
WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY?
DO WE HAVE EFFECTIVE DRUGS FOR CANCER OF UNKNOWN PRIMARY OR WE JUST HAVE RESPONSIVE SUBSETS OF PATIENTS?
DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CANCER OF AN UNKNOWN PRIMARY

N. Pavlidis, E. Briasoulis, J. Hainsworth, E.A. Greco
CUP

FAVOURABLE OR GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR POOR PROGNOSIS SUBSETS
THE FAVOURABLE SUBSETS OR GOOD PROGNOSIS SUBSETS

20% of all CUP Cases
**Favourable Subsets**

1. Women with adenocarcinoma involving only *axillary* lymph nodes.
2. Women with *papillary* adenocarcinoma of peritoneal cavity. (Primary peritoneal carcinoma)
3. *Squamous* cell carcinoma involving cervical lymph nodes
4. Poorly differentiated *neuroendocrine* carcinomas.
5. Men with blastic bone metastases and elevated PSA (adenocarcinoma)
6. Isolated *inguinal* adenopathy (squamous carcinoma).
7. Patients with a *single*, small, potentially resectable tumor.

WOMEN WITH OCCULT PRIMARY BREAST CARCINOMA PRESENTING AS AXILLARY LYMPHADENOPATHY
Subset 1

Women with adenocarcinoma involving axillary nodes

• Mostly ductal adenocarcinoma (ER/PR 40%, HER2 30%)

• Mean age 52 years. Postmenopausal 66%.

• Should be managed as stage II breast cancers (axillary dissection, ipsilateral breast radiotherapy, adjuvant chemo/hormone therapy)

• Distant metastases in < 2%

• 5-year survival: 72%

Pentheroudakis G, Lazaridis G, Pavlidis N
Women with Serous Papillary Peritoneal Carcinoma (Primary Peritoneal Carcinoma)
Women with primary papillary adenocarcinoma peritoneal cavity

- Similar presentation with advanced ovarian cancer.
- Median age 60 years
- Histopathology: serous or papillary adenoCa
- Serum CA125 is frequently increased
- Should be treated as stage III-IV ovarian cancer (cytoreduction, followed by platinum / taxanes)
- Responses: 80% (CR: 30-40%), Median survival: 36 months
SQUAMOUS CELL CARCINOMA OF AN UNKNOWN PRIMARY SITE INVOLVING CERVICAL LYMPH NODES
Squamous cell carcinoma involving cervical nodes

• It constitutes the 5% of all head-neck cancers. Age 60 yrs

• INVESTIGATION OF PRIMARY SITE
  i) bilateral tonsillectomy or tongue base mucosectomy (80% sensitivity)
  ii) PET-scan to detect the primary has 80% sensitivity

• TREATMENT:
  ▪ $N_1$ or $N_{2a}$ disease without extracapsular extension: surgery alone
    [locoregional control: 80–90%, 5-yr survival: 65%]
  ▪ $N_{2b}$ stage or with extracapsular extension: Postoperative ChemoRT
HPV – RELATED SCCUP

- **DIAGNOSIS**: p16 expression and HPV-DNA (by PCR or in situ hybridization)

- **TREATMENT**: to date, the current treatment of HPV-SCCUP should not differ from the standard management of the rest of the SCCUP

- **PROGNOSIS**: from retrospective studies HPV-related SCCUP patients have a better prognosis compared to the non HPV-related SCCUP. Ongoing prospective trials are warranted

Rassy E, Pavlidis N, Head and Neck (in press), 2019
POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA OF AN UNKNOWN PRIMARY SITE

TREATMENT OF NEUROENDOCRINE CUP

Data : 1988 – 2010, 515 patients

Chemotherapy (Platinum based) : 65% treated

Response rate : 50-60% (CR: 20 - 30%)

Median survival : 15.5 months (11.6 – 40)
NEWLY IDENTIFIED FAVOURABLE CUP SUBSETS WITH THE AIM OF IMMUNOHISTOCHEMISTRY OR MOLECULAR PROFILING

1. Colon carcinoma of unknown primary (CK20+, CK7-, CDX2+)

2. Merkel cell carcinoma of unknown primary

3. Renal cell carcinoma of unknown primary

4. Lung carcinoma of unknown primary (?)

5. Metastatic melanoma of unknown primary
Subset 1a

ADENOCARCINOMA WITH A COLON – PROFILE (CK $^{20+}$, CK $^{7-}$, CDX $^{2+}$, CEA$^+$) OF AN UNKNOWN PRIMARY SITE
Treatment and Survival of CUP with a Colon Profile (CK20+, CK7-, CDX2+)

• Should be treated as advanced colorectal cancer with chemotherapy / targeting treatment

• Response Rate : 50% (CR 15%, PR 35%)

• Median Survival : 21-37 months

Clin Colorectal Cancer 11(2): 112-8, 2012
Subset 2a

Renal Cell Carcinoma Presenting as CUP
RENAL CELL CARCINOMA PRESENTING AS CUP

N Pts : 52       Median Age : 64 yrs

Histology :  Clear Cell  39%
Papillary     31.5%
Unspecified   29.5%

IHC : Vimentin, CK (AE1/AE3), CD10, CK8/18, Pax8

Targeted Rx :  Sunitinib, Pazopanib, Everolimus, Temsiroliimus

RR : 40-50%  PR
Mean PFS : 8.5 months
Mean Survival : 6-16 months
Merkel Cell Carcinoma of unknown Primary of Stage III B

ImmunoTargets and Therapy 7:15-19, 2018

88 patients with Merkel tumors treated with Avelumab: RR 33% (CR 11%)
Unknown primary Merkel cell carcinoma: 23 new cases and a review

Tina I. Tarantola, MD, Laura A. Vallow, MD, Michele Y. Halyard, MD, Roger H. Veenig, MD, Karen E. Warschaw, MD, Amy L. Weaver, MSc, Randall K. Roenigk, MD, Jerry D. Brewer, MD, and Clark C. Otley, MD
Rochester and Minneapolis, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona

- At 2 years, overall survival of patients with stage IIIB unknown primary MCC was significantly improved compared with patients with stage IIIB known primary MCC: 76.9% to 36.4% (P = .028).

Fig 1. Overall survival among 18 patients with stage IIIB unknown primary Merkel cell carcinoma (MCC) and 27 patients with stage IIIB known primary MCC from same time period. Kaplan-Meier estimates are provided at 1, 2, 3, 4, and 5 years. Number at risk are included in parentheses.
Subset 4a

METASTATIC MELANOMA OF UNKNOWN PRIMARY
MALIGNANT MELANOMA OF UNKNOWN PRIMARY SITE:
TO MAKE THE LONG STORY SHORT.
A SYSTEMATIC REVIEW OF 4,348 PATIENTS

Kamposioras K, Pentheroudakis G, Pavlidis N

CONCLUSIONS:

<table>
<thead>
<tr>
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<th>5 - YRS OS</th>
<th>10 - YRS OS</th>
</tr>
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<tbody>
<tr>
<td>MUP (Unknown)</td>
<td>76 %</td>
<td>63 %</td>
</tr>
<tr>
<td>MKP (Known)</td>
<td>29 %</td>
<td>19 %</td>
</tr>
</tbody>
</table>
Metastatic Melanomas of Unknown Primary Show Better Prognosis than those of Known Primary: A Systemic Review and Meta-Analysis

**J Am Acad Dermatol 2015;72:59**

**METHODS**

- Meta-analysis/systematic review of 18 studies
- 2084 pts with melanoma of unknown primary (MUP)
- 5894 pts with melanoma of known primary (MKP)

**RESULTS**

- MUP had a better overall survival compared with MKP in stage III (p=0.010) and stage IV (p = 0.008)
THE UNFAVOURABLE SUBSETS
OR
POOR PROGNOSIS SUBSETS

80 % of all CUP Cases
**UNFAVOURABLE SUBSETS**

*(80 % OF CUP CASES)*

1. Metastatic Carcinoma to the liver and other organs

2. Non-papillary malignant ascites (adenocarcinoma)

3. Multiple cerebral metastases (adeno or squamous Ca)

4. Multiple lung/pleural metastases (adenocarcinoma)

5. Multiple metastatic bone disease (adenocarcinoma)
OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

\[ \text{No of patients} : 711 \]
\[ \text{Response rate} : < 20\% \]
\[ \text{Median survival} : 5.5 \text{ months} \]

SURVIVAL OUTCOME DIFFERENCES BASED ON TREATMENTS USED AND KNOWLEDGE OF THE PRIMARY TUMOUR SITE FOR PATIENTS WITH CANCER OF UNKNOWN AND KNOWN PRIMARY IN ONTARIO

Current Oncol 2018

• From **Ontario Cancer Registry**: 2000-2005
  45,347 (96.3%) pts with known metastatic disease and
  1,743 (3.7%) pts with CUP

• Median Survival
  a) **Known Primary**. Treated vs untreated pts: 19.0 vs 2.2 mo
  b) **CUP**. Treated vs untreated pts: 3.6 vs 1.1 mo (p<0.0001)

• Overall Median Survival
  Known vs. CUP pts: 11.9 vs 1.9 mo
Conclusion

✓ The median survival time of 12.5 months for patients who received assay-directed site-specific therapy compares favorably with previous results using empiric CUP regimens.

✓ Molecular tumor profiling contributes to the management of patients with CUP and should be a part of their standard evaluation.
OVERALL SURVIVAL: Assay-directed treatment vs. empiric treatment

<table>
<thead>
<tr>
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<th>Assay-directed (N=194)</th>
<th>Empiric (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (mo)</td>
<td>12.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Overall survival Probability</td>
<td></td>
<td>$p = 0.02$</td>
</tr>
</tbody>
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PRESENTED BY: F. Anthony Greco, MD
Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis

Interpretation: We show that the development of a DNA methylation based assay can significantly improve diagnoses of cancer of unknown primary and guide more precise therapies associated with better outcomes. Epigenetic profiling could be a useful approach to unmask the original primary tumour site of cancer of unknown primary cases and a step towards the improvement of the clinical management of these patients.
Figure: Outcome of patients with cancer of unknown primary who receive a site-specific treatment that matches the EPCUP prediction.
<table>
<thead>
<tr>
<th>TRIAL</th>
<th>SPONSOR</th>
<th>DESIGN</th>
<th>ARMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEFCAPI 04</td>
<td>GEFCAPI France</td>
<td>Phase III</td>
<td>Platinum-based Cx vs Pathwork-based Rx</td>
</tr>
<tr>
<td>CUPISCO</td>
<td>ROCHE</td>
<td>Phase II</td>
<td>Platinum-based Cx vs Targeted Rx or Immunotherapy (Atezolizumab)</td>
</tr>
</tbody>
</table>
Randomized Phase II Trial Comparing Site-Specific Treatment (SST) Based on Gene Expression Profiling With Empirical Carboplatin/Paclitaxel (ECP) for Patients with CUP [OSAKA JAPAN]

- The primary end point was 1-year survival rate.
- 130 pts were randomly assigned.

**RESULTS**

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<thead>
<tr>
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<th>SST (site specific)</th>
<th>ECP (empirical)</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>5.1 m</td>
<td>4.8 m</td>
</tr>
<tr>
<td>OS</td>
<td>9.8 m (p=0.890)</td>
<td>12.5 m (p=0.550)</td>
</tr>
<tr>
<td>1-YR OS</td>
<td>44%</td>
<td>54.9% (p=0.264)</td>
</tr>
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</table>

**CONCLUSION:**

- Site-specific treatment that was based on microarray profiling did not result in a significant improvement in 1-year survival compared with empirical PC.
Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities (IHC and GEP) on a case–by–case basis, with the best possible individualized patient outcome in mind...
TARGETED THERAPY IN PATIENTS WITH CANCER OF UNKNOWN PRIMARY ORIGIN:

Where do we stand today?

Rassy E, Pavlidis N Cancer Treat Rev 67:21-28, 2018
GENOMIC ALTERATIONS IN CUP

Cancer Medicine 7:4814-4824, 2018

• METHODS: 10 peer-reviewed publications (2013-2018) of comprehensive genomic profiling in CUP patients

• FINDINGS: 85% clinically relevant mutations or targetable biomarkers were identified, of which 13%-64% may benefit from currently available drugs
THE FUTURE OF TARGETED THERAPY IN CUP With Positive Biomarkers

• Only anecdotal cases with TKIs, monoclonal antibodies or immune check inhibitors are available in patients with CUP

• Two ongoing prospective randomized trials are ongoing (GEFCAPI 04 and CUPISCO)
CRITICAL QUESTIONS ON DIAGNOSTIC AND THERAPEUTIC UTILITY OF MOLECULAR PROFILING (MP) IN CUP PATIENTS

Q 1 : Does MP assay, increases accuracy of identifying the primary site?

Q 2 : Does MP helps in utilizing targeted treatment?

Q 3 : Does identification of primary site improves patient outcome (survival)?
STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)

SEARCH FOR PRIMARY SITE

STEP I
Clinical, immunohistochemistry, imaging, endoscopy studies

RULE-OUT POTENTIALLY TREATABLE OR CURABLE TUMORS
(Immunohistochemistry or other studies)

i.e. Breast Cancer, Germ-cell Tumors, Lymphomas

STEP II

CHARACTERIZE THE SPECIFIC CLINICOPATHOLOGICAL ENTITY

STEP III

TREAT THE PATIENT

FAVOURABLE SUBSETS
[Similarly to relevant primaries with “Curative Intent”]

UNFAVOURABLE SUBSETS
[With empirical chemotherapy with “Palliative Intent” or with specific Rx following gene profiling]
Thank you