Cancer of Unknown Origin

When You Know That You Don’t Know:

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Definition

Carcinoma of unknown origin (CUO) is a disease in which cancer cells are found somewhere in the body, but the place where they first started growing (the origin or primary site) cannot be found.

Key Statistics

• 5% to 10% of all diagnosed cancers in US
• Occurs equally in men and women
• Average age at diagnosis is about 60 years
• At presentation, half of patients have multiple sites of involvement
Key Statistics

- ACS estimates about 28,600 people will be diagnosed in 2005
- 70% to 80% of patients will die within a year of diagnosis
- When spread is limited to 1 or 2 sites and not adenocarcinoma, half of these patients will live > 3 years

Characteristics

- Clinical absence of primary tumor
- Early dissemination
- Aggressiveness
- Unpredictability of metastatic pattern

Characteristics

- Median survival of 6-9 months
- Chromosomal abnormalities in short arm of chromosome 1
- Abnormalities in p53 gene in > 70% of patients

Clinical Presentation

- Short history of local symptoms
  - Pain, swelling, cough
- Short history of constitutional symptoms
  - Weight loss, malaise, fatigue, fever
- Obvious abnormalities on physical examination
  - Palpable lumps at a single site
  - Commonly at different sites

Serious Prognosis

- Most are fast-spreading cancers
- Difficult to know what treatment is best
- Because the cancer is usually widespread, it is rarely curable

Why Primary Cancer Cannot Be Found

- Immune system may have destroyed the primary tumor, but not the secondaries
- Secondaries may have grown and spread quickly, while the primary is still too small to be detected on x-rays or scans
Why Primary Cancer Cannot Be Found

- Primary tumor may be impossible to be seen on x-rays or scans as it is hidden by several larger secondaries that have grown close to it
- Tumors of the lining of the digestive system may have passed out of the body through the bowel

Management

- What is the appropriate evaluation?
  - Role of pathology?
  - Role of specific radiographic studies?
  - Role of tumor markers?

Management

- What is the appropriate treatment?
  - Should all patients receive similar therapy?
  - How can therapy be individualized?
    - Prognostic subgroups

Management

- Are there strategies to suggest probable primary?
  - Metastatic patterns
  - Microarray

Evaluation

Biopsy of metastatic site should be performed early in the diagnostic process to guide further work-up.

Types of Biopsies

- Fine needle aspiration (FNA)
- Core needle
- Excisional
- Incisional
Biopsy Sample Analysis

- Immunohistochemistry
- Electron microscopy
- Flow cytometry

Biopsy Sample Analysis

- Cytogenetics
  - Fluorescence in situ hybridization (FISH)
- Molecular genetic testing
- Gene expression

Imaging Studies

- Chest x-ray
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Symptom-directed endoscopy
  - Colonoscopy
  - Fiberoptic laryngoscopy
  - Bronchoscopy

Imaging Studies

Radionuclide studies

- Bone scanning
  - Recommended for evaluation of symptoms possibly related to bone metastases, not as a screening test
- $^{111}$Iridium octreotide scan
  - Reported as diagnostic of primary neuroendocrine and breast carcinomas*, but role as a screening test is unclear


Special Studies

- Serum tumor markers
  - PSA
  - CEA
  - CA-125, CA 19-9, CA 15-3
  - hCG
  - AFP
  - Paracentesis or thoracentesis
- Bone marrow aspiration or biopsy

National Comprehensive Cancer Network (NCCN) Guidelines

Clinical Practice Guidelines in Oncology
Guidelines for Treatment of Cancer by Site
Occult Primary - Version 1.2005
Guidelines for Supportive Care
Distress Management - Version 1.2005
Evaluation

- Thorough history
- Complete physical
  - Including head and neck, rectal, pelvic, and breast examinations
- Chest x-rays
- Complete blood count
- Urinalysis
- Examination of stool for occult blood
- Biopsy of the tumor

Prognostic Signs

Favorable

- Lymph node involvement
- Neuroendocrine histology

Unfavorable

- Male
- Number of organs involved
- Adenocarcinoma histology
- Hepatic and adrenal involvement

Prognostic Signs

Favorable Histology

- Poorly differentiated carcinoma with midline distribution
- Women with papillary adenocarcinoma of peritoneal cavity
- Women with adenocarcinoma involving only axillary lymph nodes
- Squamous cell carcinoma involving cervical lymph nodes
- Isolated inguinal adenopathy (squamous carcinoma)

Unfavorable Histology

- Adenocarcinoma metastatic to the liver or other organs
- Non-papillary malignant ascites (adenocarcinoma)
- Multiple cerebral metastases (adeno- or squamous carcinoma)
- Multiple lung/pleural metastases (adenocarcinoma)
- Multiple metastatic bone disease (adenocarcinoma)

Most Likely Primary Sites

- Lung and pancreas are most common primary sites
- Colorectal, breast, and prostate are other infrequent sites
**Patterns of Spread**

- Lung metastases are twice as common from primary sites found above the diaphragm.
- Liver metastases are more common from primary disease below the diaphragm.

**Clinical Prognostic Factors**

<table>
<thead>
<tr>
<th>Pathologic Subset</th>
<th>%</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>Squamous</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>5</td>
<td>33</td>
</tr>
</tbody>
</table>

**Common Presentations**

- Cervical lymph nodes
- Poorly differentiated carcinomas
- Metastatic melanoma to a single nodal site
- Isolated axillary metastasis
- Inguinal node metastasis

**Cervical Lymph Nodes**

- Careful head, neck and lung evaluation
- CT and/or MRI of head and neck
- Blinded biopsies of nasopharynx and tongue base
- Tonsillectomy recommended in pts with squamous cell or undifferentiated carcinoma

**Cervical Lymph Nodes Continued**

- If no primary site determined, may consider
  - Radical radiation therapy
  - Preoperative radiation therapy followed by radical neck dissection
  - Radical neck dissection
  - Radical neck dissection followed by postoperative radiation therapy to possible sites of origin

**Cervical Lymph Nodes Continued**

- Metastatic adenocarcinoma is associated with poor prognosis
- 3 year survival rate from 35%–59% in patients with squamous or undifferentiated tumors are treated with radical radiation therapy, surgery, or both
Poorly Differentiated Carcinomas

Subpopulation of potentially curable patients with 1 or more of the following:
• Aged younger than 50 years
• Midline tumor distribution, multiple pulmonary nodules or lymph nodes, elevated hCG or AFP serum levels
• Cells positive for hCG or AFP immunohistochemical stain

Metastatic Melanoma to a Single Nodal Site

• 5% of patients present with no detectable primary site
• Pattern of nodal spread generally follows predicted pattern for females and males with inguinal and axillary adenopathy

Isolated Axillary Metastasis

• Most likely diagnosis will be breast cancer
• Lung cancer also high
• Mammography, MRI, ER/PR present

Patients should have a radical lymph node dissection which may yield a slightly better survival than patients with Stage II or a documented primary site of melanoma

If breast and lung cancer ruled out as primary site, following treatment options may be considered:
• Lymph node dissection without mastectomy or radiation therapy to the breast with curative intent
• Same as above plus adjuvant chemotherapy
• 2 to 10 year survival in approximately 10% of patients when treated with local excision or as having primary breast cancer
**Inguinal Node Metastasis**

- Occurs in approximately 1% to 3.5% of patients
- Diagnostic excisional node biopsy
- Most common diagnosis is Hodgkin's disease or non-Hodgkin's lymphoma
- Treatment options include:
  - Local excision
  - Superficial groin dissection alone
  - Local excisional biopsy with or without radiation, inguinal node dissection, or chemotherapy
- Squamous carcinoma almost always metastatic from genital or anal/rectal area

**Inguinal Node Metastasis Continued**

- Treatment options include:
  - Local excision
  - Superficial groin dissection alone
  - Local excisional biopsy with or without radiation, inguinal node dissection, or chemotherapy
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**Special Populations**

- Breast, prostate, ovarian, and thyroid cancers are all treatable malignancies, even when metastatic
  - Represent 15% of all tumors of unknown origin

**Special Populations Continued**

- Pattern of spread is atypical
  - Prostate cancer has high incidence of metastases to nonosseous sites (lung, liver, brain)
  - Thyroid cancer may present as lung metastases

**Management**

- Identify specific treatable subgroups
  - Clinical features
  - Pathologic features
- Trial of empiric chemotherapy for patients who do not fit into any subgroup

**Favorable Clinical Subsets**

1. Squamous carcinoma involving mid-high cervical nodes
2. Women with isolated axillary adenopathy
3. Women with peritoneal carcinomatosis
4. Patients with poorly differentiated carcinoma
5. Poorly differentiated neuroendocrine carcinoma
Cervical Adenopathy
Squamous Carcinoma

• Additional workup:
  • ENT endoscopic evaluation with biopsy
  • CT chest/bronchoscopy (lower cervical/supraclavicular nodes only)
  • PET scan
• Treatment: Follow guidelines for stage III/IV head/neck cancer
  • Concurrent radiotherapy + chemotherapy

Adenocarcinoma
Involving Axillary Nodes in Females

• Additional workup (after mammogram negative):
  • ER/PR staining on biopsy specimen
  • ?MRI of breast

Adenocarcinoma
Involving Axillary Nodes in Females
Continued

• Treatment: Follow guidelines for stage II breast cancer
  • Mastectomy or axillary LND + breast RT
  • Adjuvant therapy (based on number of nodes, ER stains, etc.)

Peritoneal Carcinomatosis in Females

• Treatment - Follow guidelines for Stage III or IV ovarian cancer
  • Surgical cytoreduction
  • Chemotherapy (taxane/platinum)
  • CA-125 almost always useful in following disease status and response to treatment

Single Metastatic Lesion

• Variety of sites described (lymph node, lung, brain, liver, adrenal, bone, subcutaneous)
• Treatment: Definitive local therapy (resection and/or radiotherapy)
• ? Chemotherapy

Adult Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
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<tbody>
<tr>
<td>Carcinoid tumor</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Islet cell tumor</td>
<td>Extrapulmonary small cell</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma of thyroid</td>
<td>Peripheral neuroepithelioma</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>Merkel cell tumor</td>
</tr>
<tr>
<td>Adult neuroblastoma</td>
<td></td>
</tr>
</tbody>
</table>
Young Men with Clinical Features of Extragonadal Germ Cell Tumor

- Additional workup:
  - Serum HCG, AFP
  - Testicular US (with retroperitoneal tumors)
  - Consider molecular genetic analysis for chromosome 12
- Treatment: Follow guidelines for EGCT
  - Cisplatin/etoposide/bleomycin x 4 cycles

Adenocarcinoma (well differentiated)

- Typical Patient
  - Elderly
  - Multiple metastatic sites (liver, bone, lung are common sites)
  - Poor response to treatment
  - Median survival is 3-4 months

Empiric Therapy

- Recent regimens incorporating new agents are more effective (higher response rates, probably improved survival)
- Recent regimens excluding cisplatin are less toxic, more convenient, outpatient

Empiric Therapy Continued

- Most patients should receive a trial of empiric therapy
- Other new drugs/combinations need further evaluation
- Randomized trials should be considered

Treatment

- Alone or in combination
  - Surgery
  - Radiation therapy
  - Chemotherapy
  - Hormone therapy
  - Clinical trials

Two Truths

- For most solid tumors that have metastasized, chemotherapy is only palliative and does not significantly improve long-term survival.
- Occult primaries can metastasize to any site and one cannot rely on patterns of metastases to determine the primary site.
More to Come!

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Case Study
• A.K. 36 year old female
• Presented to her local physician 9/02
  • Reports:
    • Fatigue x 5 months
    • Abdominal distention x 4 months

Initial Diagnostic Work-up
• Lab work:
  • Ca = 13.1
  • LFTs elevated
• Abdominal Ultrasound ➔ Liver mass
• CT scan of chest, abdomen & pelvis
  • Liver nodules replacing ¾ of liver
  • Multiple lung lesions bilaterally (<1cm)
• Liver biopsy
  • Moderately differentiated adenocarcinoma unknown primary

Work up (Continued)
• Endoscopy ➔ mild gastritis
• Colonoscopy ➔ negative
• Mammogram ➔ negative
• Pap Smear ➔ negative
• Bone scan ➔ WNL

Initial Consult at MSKCC (10/02)
• Review of systems
  • Early satiety
  • Weight loss (6lbs)
  • Pain (RUQ)
  • Constipation
  • Fatigue
• Physical Exam ➔ WNL except:
  • Enlarged liver/spleen
• PS = 90% (Karnofsky)
Patient’s History

- Past medical history
  - 3 children: 15 months, 5 & 7 years old
- Social history
  - Non-smoker
  - Social drinker
  - No recreational drug use
- Family history
  - Maternal grandmother died of colon cancer at age 63

Medications

- Duragesic 25 mcg patch
- Tylenol with codeine q 4 hrs prn pain
- Zolpidem tartrate (Ambien) 10 mg q hs
- Alprazolam (Xanax) 0.5 mg prn anxiety
- Gas X

Tumor Markers

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>10/02</th>
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<tbody>
<tr>
<td>CEA</td>
<td>0 - 5 ng/ml</td>
<td>0.9</td>
</tr>
<tr>
<td>AFP</td>
<td>0 - 15 ng/ml</td>
<td>3.7</td>
</tr>
<tr>
<td>CA 15 - 3</td>
<td>0 - 36 Units/ml</td>
<td>57</td>
</tr>
<tr>
<td>CA 125</td>
<td>0 - 35 Units/ml</td>
<td>58</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>0 - 33 Units/ml</td>
<td>37</td>
</tr>
</tbody>
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Review of Pathology
(liver biopsy)

- Moderately differentiated adenocarcinoma of unknown primary
- Immunohistochemical stains
- Re-review of pathology
- Additional work-up rule out neuroendocrine tumor
  - Parathyroid hormone level
  - Pancreatic polypeptide level
- Diagnosis: Most consistent with pancreaticobiliary primary

Potential Diagnosis Included:

1. Carcinoid Tumor
2. Metastatic Adenocarcinoma of Peritoneum
3. Colorectal Cancer
4. Pancreatic Carcinoma
5. Primary Cholangiocarcinoma

Prognostic Factors

- Favorable
  → Good performance status
  → Non-smoker
- Unfavorable
  → Adenocarcinoma
  → Multiple sites
  → Lung
  → Liver
**Initial Treatment Discussion**
- No surgical or radiation options
- Systemic chemotherapy
  - Gemcitabine 1250 mg/m² D 1 & 8 q 21 days
- Zoledronic acid q 4 weeks
- Discussed supportive care issues
  - Advanced directives

**1st Regimen**
- 3 cycles of Gemcitabine 1250 mg/m² q 21 days
  - 10/21 - 12/9/02
  - Dose reduction by 20% to thrombocytopenia
  - Changed to weekly regimen at lower dose 12/9
- Reassessment (12/02)
  - Stable disease on CT scan
  - RUQ pain relieved
  - Mild fatigue with active lifestyle
  - 3 lb weight loss

**Decision Making**
- Pt investigated:
  - Surgical options
  - Clinical Trials
- Patient’s Goal:
  - Better response than stable disease
  - Wanted more aggressive management

**2nd Regimen**
- Pt opted for Clinical Trial:
  - Irinotecan 180 mg/m² q 14 days
  - Leucovorin 400 mg/m² q 14 days
  - Fluorouracil
    - 400 mg/m² IVP Day 1
    - 1800 mg/m² continuous infusion X 48 hours
  - Flavopiridol 50 mg/m² q 14 days
    (7 hours after irinotecan)
- Received 1 cycle

**Novel Agent Flavopiridol**
- Side effects:
  - Nausea & vomiting
  - Diarrhea
  - Bone marrow suppression
  - Hypotension
  - Fatigue
  - Anorexia/weight loss
  - Flu-like symptoms
  - Pericarditis/Pericardial effusion/tamponade
March 2003 Work Up:

- Pt had:
  - Increased fatigue
  - Decreased appetite
  - Ascites
  - Increased LFT’s & Ca++
- CT scan ➔ progression (liver)
- OctreoScan ➔ negative
- Bone marrow examination (thrombocytopenia)
- PET Scan ➔ liver and lung metastases
- Lung biopsy

Lung Biopsy

- Well-circumscribed nodule surrounded by normal lung parenchyma
- CK20+
- Negative
  - CK7
  - TTF1
  - 34BE12
  - ER, PR, Her-2, BR2

3rd Regimen

- Pursued alternative options
- Gemcitabine 750 mg/m² on day 1 & 8
- Docetaxel 75 mg/m² on day 8
  - 4/03 – 3/16/04 (total of 13 cycles)
- Started on erythropoietin in July 2003
- Continued on zoledronic acid
- Encouraged by clinical improvement
- Patient scheduled a vacation
- Developed SOB ➔ pleural effusion ➔ cytology negative

Nursing Management

Problem: Peripheral Neuropathy

- Assessment
- Risk factors
- Avoid extreme temperature
- Assistive devices
- Manage pain

4th Regimen

- Gemcitabine 800mg/m² on day 1
- Oxaliplatin 80mg/m² on day 2
  - 4/16 - 6/25/04 (6 cycles)
- Had improvement in hepatic mets, stable lung disease (6/10)
- 6/25 Hypersensitivity reaction
  - ? Re-challenge vs. change treatment

5th Regimen

- Gemcitabine 800mg/ m² q 21D
- Capecitabine 1500mg po BID x 14 days
  - 7/8 - 11/18/04 (6 cycles)
- Planned a vacation
- Re imaging studies
- Progression of disease
**Nursing Management**

**Problem: Hand / Foot Syndrome**
- Assessment/Prevention
- Treatment
  - Cold compresses
  - Elevate affected area
  - Moisturizer / creams
  - Administer vitamin B₆ (pyridoxine) 50 mg TID
  - Pain control

**Problem: Mucositis**
- Assessment/risk factors
- Oral care
- Pain medication
- Patient education

**6th Regimen**
- Liposomal doxorubicin 35 mg/m² on 12/9/04
- Progression of disease
- Multiple system organ failure
- Final admission 12/04

**Timeline: A.K.**

**Diagnosis**
1. gemcitabine 4 cycles
2. irinotecan, leucovorin, 5FU, flavopiridol 1 cycle
3. gemcitabine, docetaxel 13 cycles
4. gemcitabine, oxaliplatin 6 cycles
5. docetaxel, capecitabine 6 cycles
6. liposomal doxorubicin 1 cycle

**Autopsy**
- Moderately differentiated adenocarcinoma of unknown primary
- Hepatic tumor shows glandular proliferation pattern with prominent stromal reaction & perineural invasion
- Pulmonary & paratracheal nodules share a similar morphology-primary hepatic tumor
- Positive for CK7
- Negative TTF-1, PE10 & CK20
- Diagnosis: cholangiocarcinoma
When You Know That You Don’t Know:
Cancer of Unknown Origin

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R.M. is a retired physician with a strong family history of breast cancer and a personal history of melanoma 37 years ago. Patient presented confused and in respiratory distress to the ED and was found to have bilateral chylous effusions. Thorascopic biopsy revealed a cancer of unknown origin.

Work-up
- History and physical exam
- CBC, electrolytes, liver function tests
- Creatinine, calcium
- Urinalysis
- Chest x-ray
- Fecal occult blood testing
- Biopsy of most accessible site

Nursing Intervention
Provide in-depth education about work-up
Diagnosis

- Special stains and procedures performed on patient
- Findings continued to be carcinoma of unknown origin
- Look at clinical presentation:
  - Chest disease indicates need for chest and abdominal CT scan, CA-125, ER/PR, mammogram, GYN consult

Choice of Treatment

- Patient’s diagnosis continued to be carcinoma of unknown origin
- KPS=40%
- NCCN 2005 guidelines indicate the need for:
  - Symptom control
  - Clinical trial if available and eligible
  - Chemotherapy in symptomatic patients

What treatments have been used?

- NCCN guidelines note that a Cisplatin based combination for this type of patient can be helpful
- Hainsworth (1997) recommends combination therapy with Taxol plus a platinum drug with or without Etoposide

Treatment

- Patient chose Carboplatin + Taxol (Hainsworth, 1997)
- In multiple studies done in the 1980s, overall response rate to platinum based chemotherapy was < 30% with a median survival time of 5-7 months (NCCN, 2004)

What is New?

- Allogeneic Peripheral Blood Stem Cell Transplantation and Donor Lymphocyte Infusions
- Irinotecan followed by Fluorouracil and Leucovorin
- Sorafenib and Bevacizumab
- Capecitabine combined with Cisplatin (NCI website, 2/13/05)
Psychosocial Assessment

- Patients and families deal with uncertainty
- Result may be significant distress

Psychosocial Assessment

- NCCN defines distress as a “multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and or spiritual nature that may interfere with the ability to cope...” (NCCN, 2005)

Psychosocial Assessment

- Use NCCN distress screening tool
- Patient or family member needs to be assessed for more serious causes of distress such as psychiatric illness or substance abuse

Psychosocial Assessment

- If patient score is >5/10, follow guideline and refer to social work, pastoral care or a therapist
- If patient's score is <5/10 usual support measures should suffice
Counseling foci

- Support should touch upon
  - Distress
  - Behavioral symptoms
  - Psychiatric history & therapy
  - Pain and symptom control
  - Body image/sexuality
  - Impaired capacity
  - Safety

Psychosocial Support by team

- What are the signs and symptoms of “normal fear, worry and uncertainty”?

Signs of “Normal” Distress

- Concerns about illness
- Sadness about loss of usual health/role change
- Anger/lack of control
- Poor sleep, appetite, concentration
- Preoccupation with illness and death (NCCN, 2005)

Focusing Psychosocial Interventions

- When are patients, family members, significant others most vulnerable to distress?

Times of Greater Distress

- Finding a new symptom or lump
- During work-up
- Awaiting diagnosis or treatment
- Change/withdrawal
- Discharge from the hospital

Times of Greater Distress

- Stresses of survivorship
- Medical follow-up and surveillance
- Treatment failure
- Recurrence or progression
- End of life

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Interventions for Distress

• Provide informational support
• Educate patient and family about times of greater distress
• Acknowledge distress
• Build trust
• Ensure continuity of care

Interventions for Distress Continued

• Exercise
• Consider medication
• Treat pain
• Refer to sources of support – individual group, religious
• Teach relaxation, meditation, creative therapies

Nursing Interventions

• Teach patient, family, significant others the signs and symptoms to report
• Educate about side effects of treatment and their management

Nursing Interventions

• Ensure that all options are presented
• Reassure patient that he/she will be cared for whatever option is chosen

Follow-up

• In some cases, due to performance status, extent of disease or patient preference, treatment may not be given
• History and physical every 2-3 months for the first 18 months, then every 3-4 months
• Symptom management
• Psychological support

Future Directions

• Developing tools for better detection and/or classification (MRI, PET)
• Identification of treatable subsets
• Treatment should be tumor of unknown origin specific

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Future Directions
Continued

• Research to focus on metastatic genotype and phenotype
• Detection of biochemical or molecular targets for treatment
• Clinical trials with novel therapies