Precursors of endometrioid carcinoma of the uterus  
“State of the Art”*

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Hershey, PA

*and clearly, it is art, not science

Disclosure
Consultant for Becker (NSF International)  
for cervical cancer screening

Learning objectives
the participant should understand the following issues relating to precursors of endometrioid adenocarcinoma

1) Natural history  
2) The lexicon  
3) Diagnostic reproducibility  
4) Current practice  
5) Recommended terminology  
WHO 2014

Problems in Defining the Natural History of Hyperplasia

1) pathologic criteria - criteria and diagnostic terminology for the various forms of hyperplasia have changed repeatedly  
2) initial sampling - the method of initial diagnosis is biopsy or curettage, which removes some or all of the lesion to be studied
Problems in Defining the Natural History of Hyperplasia

3) Coexisting lesions - other lesions such as adenocarcinoma may coexist at the time of diagnosis without our knowledge, since the D&C or biopsy samples only a portion of the endometrium.

4) Subsequent intervention - hormonal or surgical intervention usually interrupts observations of the natural history of hyperplasia.

What do we know?

Etiology and Natural History of Hyperplasia

1) Endometrial hyperplasia usually occurs in the setting of unopposed estrogen stimulation.

2) Some hyperplasias regress if the estrogenic stimulation is withdrawn or in response to progestin therapy.

3) Some hyperplasias progress to adenocarcinoma in time.

Etiology and Natural History of Hyperplasia

4) The frequency of hyperplasia is about 20X that of endometrial carcinoma.

5) The probability of progression to adenocarcinoma is related to the degree of cytologic atypia in the hyperplasia.

6) The majority of adenocarcinomas which arise in a background of hyperplasia are well differentiated, rarely lethal, and often may respond to progestin therapy.

Regression of hyperplasia following hormonal therapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Lesion response</th>
<th>Persistence</th>
<th>Progression</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kistner</td>
<td>Hyper/CIS</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Steiner</td>
<td>Hyper/CIS</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kjorstad</td>
<td>Atypical</td>
<td>41%</td>
<td>23%</td>
<td>35%</td>
</tr>
<tr>
<td>Wentz</td>
<td>Hyper/atypical</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wentz</td>
<td>Hyper/atypical</td>
<td>98%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Kurman</td>
<td>Non-atypical</td>
<td>77%</td>
<td>31%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>50%</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Gal</td>
<td>Hyper/atypical</td>
<td>92%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Huang</td>
<td>Hyper/atypical</td>
<td>52%</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>Ferenczy</td>
<td>Non-atypical</td>
<td>80%</td>
<td>20%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>0%</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Randall</td>
<td>Atypical</td>
<td>94%</td>
<td>6%</td>
<td>0</td>
</tr>
</tbody>
</table>
Progression of hyperplasia to carcinoma

Non atypical hyperplasia 3-12%
Atypical hyperplasia 25-27%

(Retrospective studies, +/- intervening therapy, incomplete follow-up of 1-20 years)

Absolute risk of endometrial carcinoma during 20 year follow-up among women with endometrial hyperplasia
Lacey et al, JCO, 2010

7900 women diagnosed with hyperplasia in a prepaid health plan; 19 years follow-up

Cumulative progression risk
Non-atypical hyperplasia 5%
Atypical hyperplasia 28%

*retrospective review, intervening hormonal therapy, D&C

Coexistence of carcinoma with atypical hyperplasia - carcinoma found in hysterectomies (within 12 weeks of initial diagnosis*)

<table>
<thead>
<tr>
<th>Author</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gusberg and Kaplan*</td>
<td>21%</td>
</tr>
<tr>
<td>Tavassoli and Kraus*</td>
<td>25%</td>
</tr>
<tr>
<td>Kurman and Norris*</td>
<td>17%</td>
</tr>
<tr>
<td>Janicek and Rosenshein*</td>
<td>43%</td>
</tr>
<tr>
<td>Leitao et al</td>
<td>34%</td>
</tr>
</tbody>
</table>

(potential bias: these studies were retrospective)

$^{*}$prospective Gynecologic Oncology Group study, using community diagnosis of atypical hyperplasia.
Typical or atypical?
Diagnostic reproducibility

Skov et al (Scandanavia)
Kendall et al (US - Hopkins)
Bergeron et al (Europe)
Zaino et al (US - G.O.G.)

Comparison of the Reproducibility of the WHO Classifications of 1975 and 1994 of Endometrial Hyperplasia


Overall Agreement and $\kappa$ Values for Diagnosis of Endometrial Hyperplasia Using WHO Classifications of 1975 and 1994 by the Six Observers

<table>
<thead>
<tr>
<th></th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
<th>Round 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall agreement</td>
<td>0.47</td>
<td>0.45</td>
<td>0.51</td>
<td>0.41</td>
</tr>
<tr>
<td>$\kappa$ value</td>
<td>0.24</td>
<td>0.25</td>
<td>0.30</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Round 1 and 3, WHO 1975; Round 2 and 4, WHO 1994 classification

$kappa$ below 0.40 - fair to poor agreement,
$kappa$ values between 0.40 and 0.8 - moderate to good agreement,
$kappa$ values greater than 0.8 - excellent agreement.

Reproducibility of the Diagnosis of Endometrial Hyperplasia, Atypical Hyperplasia, and Well-Differentiated Carcinoma

Brian S. Kendall, M.D., Brigitte M. Ronnett, M.D., Christina Isacson, M.D., Kathleen R. Cho, M.D., Lora Hedrick, M.D., Marie Diener-West, Ph.D., and Robert J. Kurman, M.D.

Interobserver Agreement*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Interpretation Round 1</th>
<th>Interpretation Round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative endometrium</td>
<td>0.86</td>
<td>Almost perfect</td>
</tr>
<tr>
<td>Simple hyperplasia</td>
<td>0.66</td>
<td>Substantial</td>
</tr>
<tr>
<td>Complex hyperplasia</td>
<td>0.49</td>
<td>Moderate</td>
</tr>
<tr>
<td>Simple atypical hyperplasia</td>
<td>0.19</td>
<td>Slight</td>
</tr>
<tr>
<td>Complex atypical hyperplasia</td>
<td>0.40</td>
<td>Moderate</td>
</tr>
<tr>
<td>Well-differentiated carcinoma</td>
<td>0.79</td>
<td>Substantial</td>
</tr>
<tr>
<td>Combined (for all diagnoses)</td>
<td>0.67</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

* k values for six diagnostic categories.

Microscopic Criteria Differentiating Endometrial Hyperplasia and Adenocarcinoma

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Adenomatous Hyperplasia</th>
<th>Atypical Hyperplasia</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclei Profiles</td>
<td>Smooth and oval</td>
<td>Irregular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Size</td>
<td>Uniform</td>
<td>Large, variable</td>
<td>Large, variable, spiculated</td>
</tr>
<tr>
<td>Nucleoli size</td>
<td>Small, round</td>
<td>Large, irregular</td>
<td>Large, irregular, spiculated</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Numerous in stroma and glands</td>
<td>Numerous</td>
<td>Variable</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Abundant, amphophilic</td>
<td>Sometimes scant, may be very abundant, with dense eosinophilia</td>
<td>Scant, pale, amphophilic</td>
</tr>
<tr>
<td>Glands</td>
<td>Tall columnar, single-layered, irregular, with outpouching and infoldings</td>
<td>Stratification, loss of polarity, irregular, with intraglandular tufting but no bridging</td>
<td>Loss of polarity irregular, with cribriform pattern and intraglandular bridging</td>
</tr>
<tr>
<td>Size</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Stromal confluence</td>
<td>Usually abundant, cellular</td>
<td>Scant, with crowding</td>
<td>Scant</td>
</tr>
</tbody>
</table>


Histologic Features for Proliferative Endometrium vs. Hyperplasia*

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gland crowding</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gland branching</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Nuclear rounding</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Loss of polarity</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Nuclear enlargement</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

* Number of pathologists (of 5) showing an association by univariable and multivariable logistic regression analysis with the diagnosis of hyperplasia and the listed feature.

Histologic Features for Hyperplasia vs. Atypical Hyperplasia*

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear enlargement</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Vesicular change</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Chromatin irregularities</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Loss of polarity</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear rounding</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Glandular confluence</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

* Number of pathologists (of 5) showing an association by univariable and multivariable logistic regression analysis with the diagnosis of hyperplasia and the listed feature.
A Multicentric European Study Testing the Reproducibility of the WHO Classification of Endometrial Hyperplasia With a Proposal of a Simplified Working Classification for Biopsy and Curettage Specimens

Christine Bergeron, M.D., Ph.D., Francisco F. Nogales, M.D., Marco Masseroli, Ph.D., Vera Abeler, M.D., Pierre Duvillard, M.D., Elisabeth Müller-Holzner, M.D., Heinz Pickartz, M.D., and Michael Wells, M.D., F.R.C.Path

*The American Journal of Surgical Pathology 23(9): 1102-1108, 1999*

### Mean Intraobserver Agreement on Principal Diagnosis Based on Seven and Three Diagnostic Categories

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>% Agreement</th>
<th>Diagnostic Category</th>
<th>% Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative</td>
<td>73</td>
<td>Cyclic endometrium</td>
<td>79</td>
</tr>
<tr>
<td>Secretory</td>
<td>75</td>
<td>Hyperplasia</td>
<td>61</td>
</tr>
<tr>
<td>Other</td>
<td>29</td>
<td>Neoplasia</td>
<td>79</td>
</tr>
<tr>
<td>Simple hyperplasia</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex hyperplasia</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-differentiated carcinoma</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined†</td>
<td>74</td>
<td>Combined†</td>
<td>85</td>
</tr>
<tr>
<td>[kappa 0.68]</td>
<td></td>
<td>[kappa 0.76]</td>
<td></td>
</tr>
</tbody>
</table>

† For all diagnostic categories.

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atypical endometrial hyperplasia
306 endometrial samples
community diagnosis of AEH
Hysterectomy within 12 weeks
Independent reviews of endo sample
Panel review of hysterectomy

Panel diagnosis*  frequency  % of total
Nml                 20         7%
Hyperplasia         54         18%
AEH                 116        39%
Carcinoma           87         29%
Insufficient        3          1%
No agreement        21         7%

* Compared to community diagnosis
(2/3 or 3/3 panelists agreement)
Intra-Panel Agreement

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Kappa</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.48</td>
<td>moderate</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>0.38</td>
<td>fair</td>
</tr>
<tr>
<td>AEH</td>
<td>0.27</td>
<td>fair</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0.50</td>
<td>moderate</td>
</tr>
<tr>
<td>Unable to assess</td>
<td>0.63</td>
<td>substantial</td>
</tr>
<tr>
<td>Overall</td>
<td>0.39</td>
<td>fair</td>
</tr>
</tbody>
</table>

Diagnostic problems identified

- Application of diagnostic criteria
  - Quantitative, qualitative, multiple criteria
- Small quantity/fragmentation of tissue
- Poor fixation
- Poor cryotomy
- Poor staining

Coexistent carcinoma in the hysterectomy

Trimble et al, Cancer, 2006

Cancer in uterus

<table>
<thead>
<tr>
<th>Community diagnosis of AEH</th>
<th>43%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel diagnosis</td>
<td></td>
</tr>
<tr>
<td>Nml/typical hyperplasia</td>
<td>18%</td>
</tr>
<tr>
<td>AEH</td>
<td>43%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>65%</td>
</tr>
</tbody>
</table>

GOG Studies Conclusions

1) The reproducibility of the community diagnosis of AEH by a panel of gyn pathologists is relatively low
2) Over-estimation and under-estimation of the severity of the lesion is common
3) The reproducibility of the diagnosis of AEH by a panel of gyn pathologists is relatively low
4) The risk of carcinoma associated with the diagnosis of atypical hyperplasia is 43%
Diagnosing endometrial hyperplasia: why is it so difficult to agree?
Allison et al, AJSP, 2008

3 pathologists scored 1800 endometria
For adequacy, volume of hyperplasia, crowding, complexity, atypia, metaplasia and diagnosis (using WHO)
Kappas of 0.16 to 0.35 for hyperplasias
Due to:
1) marked diagnostic trends of 2 pathologists,
2) scant tissue
3) low volume of hyperplasia

Conclusions of current schemas for endometrial hyperplasia
1) Terminology of hyperplasia is confusing with varying usage of identical terms
2) Diagnostic reproducibility is poor
3) Carcinoma frequently coexists in the uterus with atypical hyperplasia
4) There is need for a new conceptual and practical approach to preinvasive endometrial lesions

In the future, can we distinguish lesions of high risk from those of low risk for development of cancer?

Morphometry
Tumor promoter or suppressor gene mutation
Immunohistochemistry
Analysis for clonality (neoplasm)

Morphometry - Baak et al
Assessed 22 nuclear and architectural features
Most important Discriminant factors (D-score) in prediction of lesions likely to progress to adenocarcinoma:
1) Volume percentage stroma (VPS)
2) Standard deviation of shortest nuclear axis
3) Outer surface density of glands
Morphometry - Baak et al

Lesions with a volume percentage stroma (VPS) of less than 55% are associated with an increased probability of progression to invasive carcinoma.

Estimating VPS
(http://www.endometrium.org)

70% VPS 60% VPS 40% VPS

Endometrial intraepithelial neoplasia (EIN) (Mutter & Baak, 2000)

Clonality determinations of carcinomas: selected MSI endometrial carcinomas or women who are heterozygotes at HUMARA (human androgen receptor) on chromosome X examined adjacent “endometrial hyperplasia” to determine if clonal:

<table>
<thead>
<tr>
<th>Polyclonal</th>
<th>Monoclonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High D-score</td>
<td>Low D-score</td>
</tr>
<tr>
<td>VPS &gt;55%</td>
<td>VPS &lt;55%</td>
</tr>
<tr>
<td>(hyperplasia)</td>
<td>(EIN)</td>
</tr>
</tbody>
</table>

EIN Criteria (all must be met)
http://www.endometrium.org

Architecture
Area of Glands>Stroma (VPS<55%)

Cytology
Cytology differs between architecturally crowded focus and background.

Size
Maximum linear dimension exceeds 1mm.

Exclude mimics
Benign conditions with overlapping criteria: basalis, secretory, polyps, repair, etc..

Exclude cancer
Maze-like glands, solid or cribriform growth
Endometrial intraepithelial neoplasia
PTEN
Mutter et al

PTEN - tumor suppressor gene, lipid phosphatase crucial in cell survival signal transduction pathway;
most common mutation or deletion in hyperplasia or endometrioid adenocarcinoma (early loss)

Loss of PTEN
Proliferative phase 0% (rare null glands)
Disordered pro/hyperplasia 10-40%
EIN 40-55%
Carcinoma > 60%
Proposed model

1) Polyclonal lesions often represent a physiologic response to continued estrogen stimulation and are not direct precancers
2) A clonal population occasionally emerges from within a subset of polyclonal lesions
3) Endometrial cancers and precancers (EIN) share a monoclonal growth pattern
4) Cancers with PTEN mutations or MSI may acquire this change as precancers
5) Monoclonal endometrial precancers have a distinctive morphology (and morphometry) of a subset of hyperplasias

Two concepts of carcinogenesis

<table>
<thead>
<tr>
<th>Continuum model</th>
<th>Discrete model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative</td>
<td>Proliferative</td>
</tr>
<tr>
<td>Disordered proliferative</td>
<td>hyperplasia</td>
</tr>
<tr>
<td>Simple hyperplasia</td>
<td>Complex hyperplasia</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>EIN</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>adenocarcinoma</td>
</tr>
</tbody>
</table>

Predictive value of EIN
(Cancer. Mutter et al, 2005)

477 hyperplastic biopsies, >1 year follow-up “progression to cancer” in 24 (5%) cases

6/354 (2%) non-atypical hyperplasia
16/123 (13%) atypical hyperplasia
11/56 (20%) complex atypical hyper

2/359 (1%) non-EIN
22/118 (19%) EIN

Should EIN be adopted?

Conceptually appealing
Reproducibility needs to be established
Predictive value needs to be assessed by other investigators
Reproducibility of EIN diagnosis is good, but influenced by the diagnostic style of pathologists. Usubutun, Mutter, et al, Mod Path, 2012

20 pathologists from Turkey and US
Kappa 0.58 (benign, EIN, cancer)
Disagreements due to a variety of diagnostic styles which were not associated with experience, practice type, institution, or diagnostic system used in practice.

Reproducibility of current classifications of endometrial endometrioid glandular proliferations; Ordi et al, Histopathology, 2013

9 expert pathologists from Europe and NA examined 198 endometrial samples

<table>
<thead>
<tr>
<th>System</th>
<th>repro (k)</th>
<th>simplified*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>0.34</td>
<td>0.59</td>
</tr>
<tr>
<td>EIN</td>
<td>0.42</td>
<td>0.59</td>
</tr>
<tr>
<td>EWG</td>
<td>0.53</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*reduces to 2 groups (benign, hyperplasia [without atypia] vs atypical hyperplasia, EIN, carcinoma, neoplasia)

Reproducibility of biopsy diagnoses of endometrial hyperplasia: evidence supporting a simplified classification. (Sherman et al, IJGP, 2008)

WHO 1994 system (209 samples)
submitting vs panel diagnosis $K = 0.17$
Panelist 1 vs 2 $K = 0.37$

Condensed system*
Submitting vs panel $K = 0.37$
Panelist 1 vs 2 $K = 0.63$

* (DP, SH, CH vs AH, CA)

What is the current diagnostic practice in the US?

Hyperplasia - common
EIN - uncommon
EIN criteria with hyperplasia terminology
- very common (in the Eastern US)
- ? (in the Western US)
Clinical management of AH/EIN
SGO practice guidelines
Trimble et al, Obstet Gynecol, 2012

Definitive therapy
Total hysterectomy +/- BSO

Non-surgical options*
Hormonal therapy (with a progestin)
Endometrial ablation not recommended
*for those desiring fertility or poor surgical candidate with co-morbidities

WHO 2014
Uterine Corpus:
Epithelial tumors and precursor lesions
Condensed to two diagnostic choices

Hyperplasia without atypia
Atypical hyperplasia/EIN

Hyperplasia without atypia

“An exaggerated proliferation of glands of irregular size and shape, with an associated increase in the gland to stromal ratio compared with proliferative endometrium, without significant cytological atypia”

Syn. Simple or complex non-atypical hyperplasia

Atypical hyperplasia/
endometrioid intraepithelial neoplasia

“Cytologic atypia superimposed on endometrial hyperplasia defines atypical hyperplasia/EIN”

Syn. Simple or complex atypical endometrial hyperplasia, endometrial intraepithelial neoplasia
Atypical hyperplasia/EIN (cont.)

“The distinction from hyperplasia without atypia is based on nuclear atypia, which may include enlargement, rounding, loss of polarity, and nucleoli. As these features are somewhat subjective, intraobserver and interobserver variability remains problematic.”

Atypical hyperplasia/EIN

“The diagnosis of atypia is facilitated by comparison to normal glands or areas of hyperplasia without atypia”

Hyperplasia/EIN conclusions

1) The prior hyperplasia classification methods were not highly reproducible
2) Lesions called hyperplasia include both polyclonal and clonal lesions
3) The binary division into hyperplasia without atypia and atypical hyperplasia/EIN improves diagnostic reproducibility

Hyperplasia/EIN conclusions

4) Clonal lesions (EIN) (many of which resemble AEH) could be considered non-invasive carcinomas
5) ~40% of AEH/EIN on biopsy have invasive carcinoma in the uterus
6) Clinical colleagues should be advised of the relatively low diagnostic reproducibility and high probability of a carcinoma in lesions called AEH
Learning objectives
the participant should understand the
following issues relating to precursors of
endometrioid adenocarcinoma

1) Natural history
2) The lexicon
3) Diagnostic reproducibility
4) Current practice
5) Recommended terminology
WHO 2014