Feasibility of Applying WHO Essential Criteria for Diagnosis of Female Genital Tumors:

Results of an International Practice Survey on Access to WHO-Required Diagnostic Immunohistochemistry and Molecular Tests

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Background

- **The international standard for pathologic classification of tumors is the WHO system**

Classifiers
Clinical features
Epidemiology
Pathogenesis
Macroscopic pathology
Histopathology
Immunophenotype
Molecular pathology

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REVIEW

Revising the WHO classification: female genital tract tumours

Ian A Cree, Valerie A White, B Iciar Indave & Dilani Lokuhetty
International Agency for Research on Cancer (IARC), World Health Organisation, Lyon, France

- **New categories of "<u>essential criteria</u>" and "<u>desirable criteria</u>" were added in the 5th WHO**
  - **No written definition of when IHC/molecular tests should be included as "essential"**
  - **Decision left to discretion of chapter authors and section editors**

Background

Questions of Interest

- **How feasible are the essential criteria to apply in terms of access to IHC/molecular tests ?**
- **Is the applicability of essential criteria associated with economic environment of the practice ?**

Aims

1. **Define the extent to which IHC / molecular tests are required as “essential criteria” in 5th WHO-Female Genital Tumors**

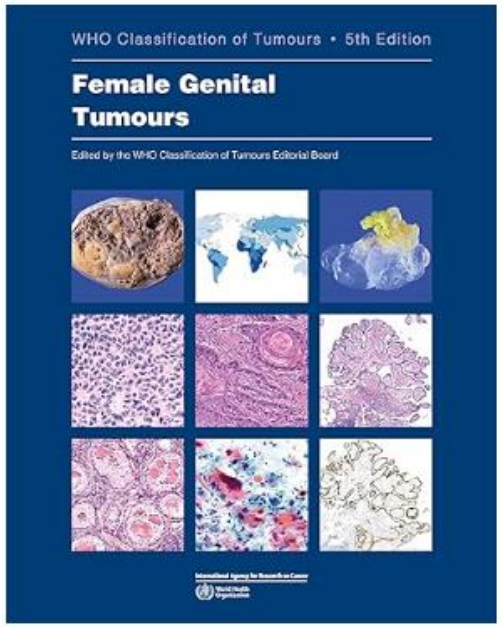
2. **Define global access to “required” IHC / molecular tests**

Methods

Step 1

Classified the requirements of “essential criteria” of each tumor in 5th WHO-Female Genital Tumors

Requirement
Immunostain ?
Molecular test ?
“Differentiation” ?



Methods

Step 1

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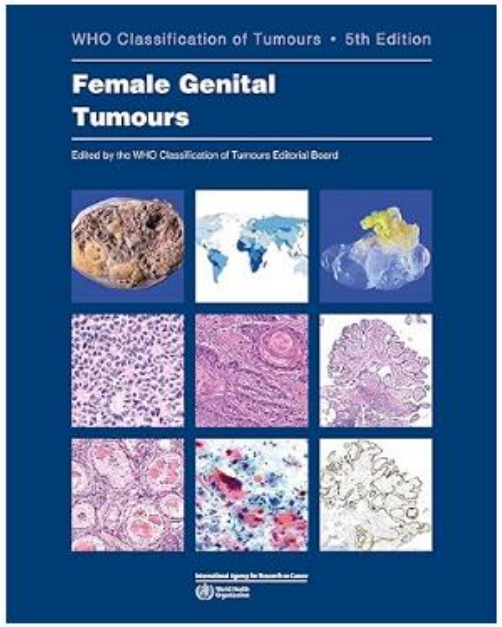


Step 2

Surveyed pathologists on their access to required immunostains / molecular tests

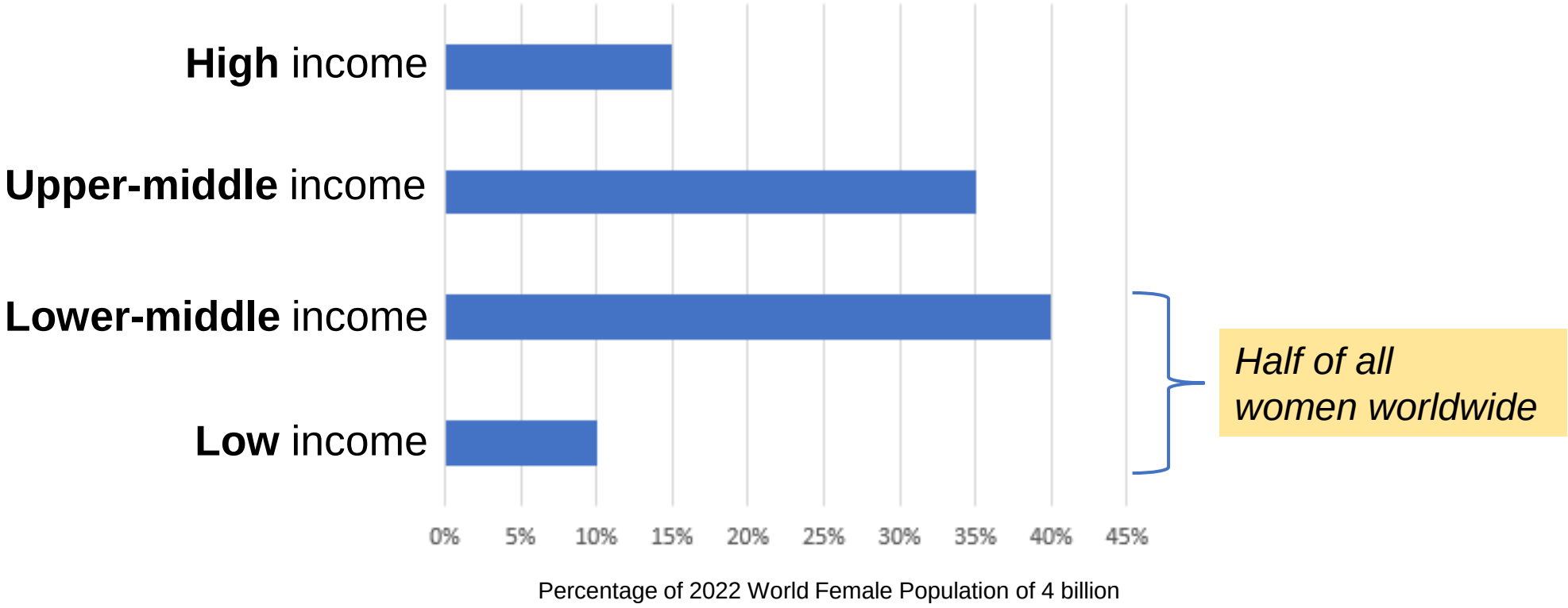
Categories of Access
Routine (inhouse/send-out)
Only with difficulty in rare cases
None

Typical Practice Style
Level of use of IHC

Recruitment of Survey Participants
▪ Registrants of ISGyP LiVE sessions
▪ ISGyP members
▪ "Friends of friends" via whatsapp, email

Methods

- Analysis of survey responses stratified by 4-tier economic categories of countries using **2022 World Bank** classification system https://databank.worldbank.org/home.aspx



Results

Required as Essential Criteria	Types	Involved tumors
Immunostain	**36**	**35**
Molecular test	**5**	**7**
“Differentiation”	**18**	**36**

Immunostains

- p16
- CD34
- Estrogen receptor
- Neuroendocrine IHC
- Progesterone receptor
- BCOR
- CD99
- D240
- EMA
- FOXL2
- inhibin
- keratin
- Ki67
- S100
- SF1
- WT1
- OCT4
- ALK
- CD117
- Chromogranin
- CK7
- CK8/18
- cyclin D1
- desmin
- DOG1
- e-cadherin
- FLI1
- GFAP
- hCG
- HLA-G
- HMB45
- HSD3B1
- MCAM
- MelanA
- MUC4
- MyoD1
- myogenin
- p53
- p63
- PLAP
- SALL4
- SMARCB1
- Smooth muscle actin
- STAT6
- synaptophysin

Molecular tests

- High risk HPV ISH
- STR genotype test
- *YWHAE* translocation
- *NTRK* translocation
- *EWSR1::FLI1* translocation

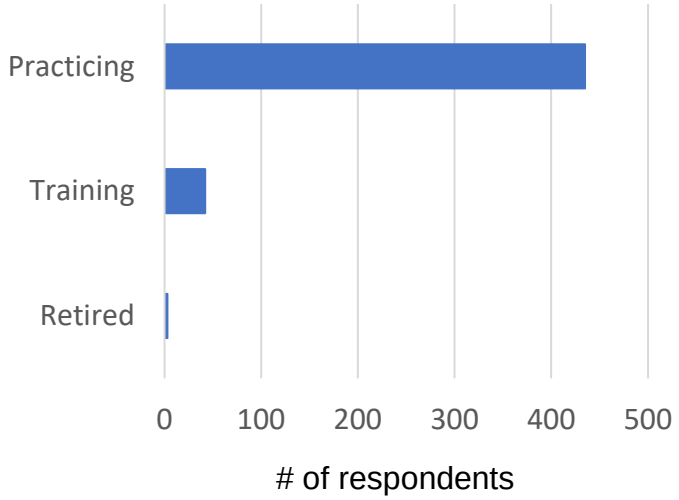
Types of Differentiation

- Germ cell differentiation
- Smooth muscle differentiation
- Clear cell differentiation
- Endometrioid differentiation
- Serous differentiation
- Urothelial differentiation
- Granulosa cell differentiation
- Intestinal differentiation
- Sex cord stromal differentiation
- Steroid cell differentiation
- Fibroblastic differentiation
- Mesonephric differentiation
- Mesothelial differentiation
- Myofibroblastic differentiation
- Prostatic differentiation
- Sertoliform differentiation
- Thyroid differentiation
- Trophoblast differentiation

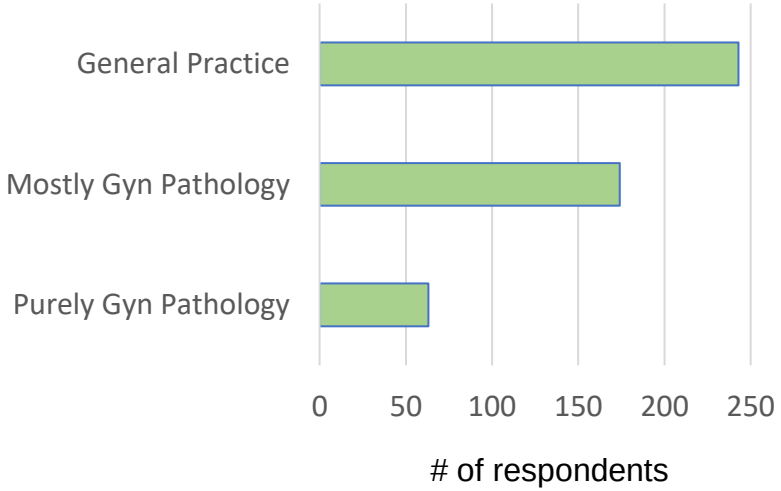
Survey Participants

Total N = 480

Career Status



Practice Case Mix



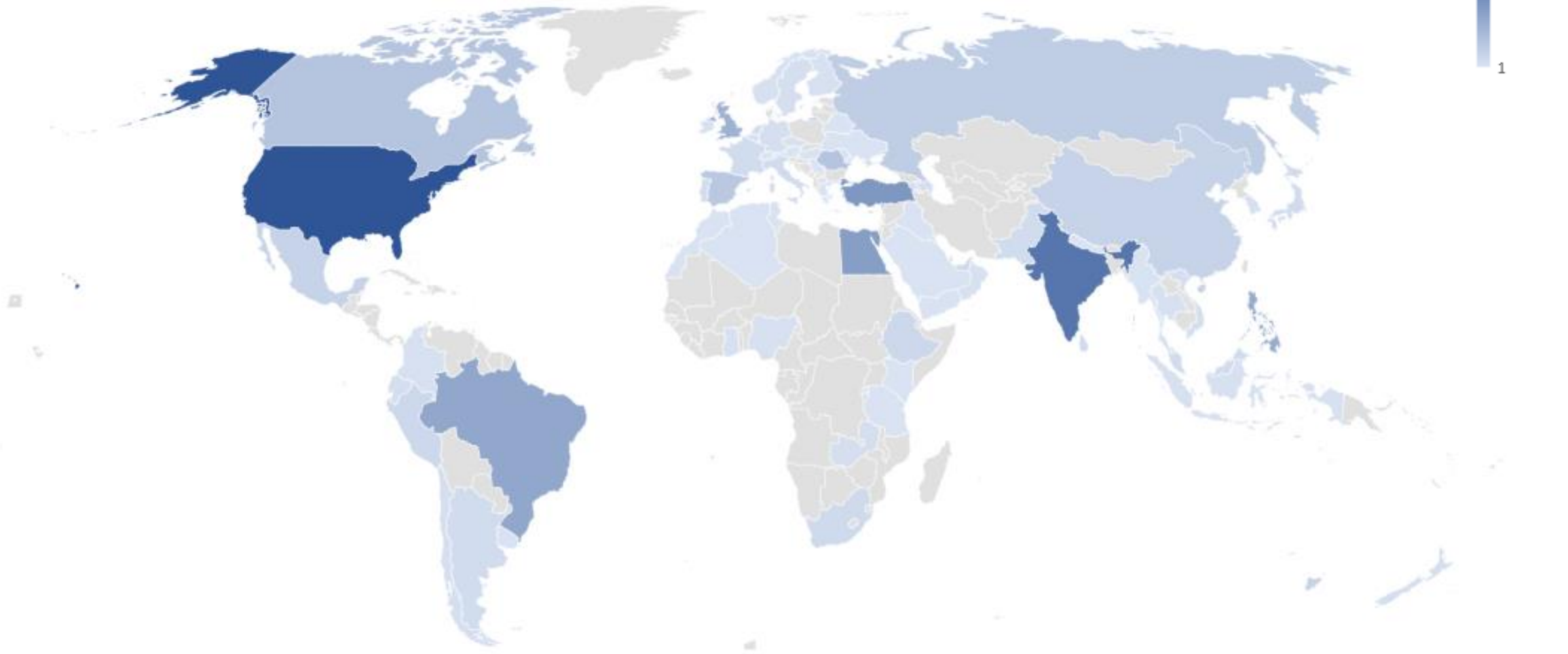
Academic Affiliation

High income	77%
Upper middle income	64%
Lower middle income	81%
Low income	86%

Generalists	
High income	37%
Upper middle income	50%
Lower middle income	69%
Low income	100%

Distribution of Survey Participants

76 countries



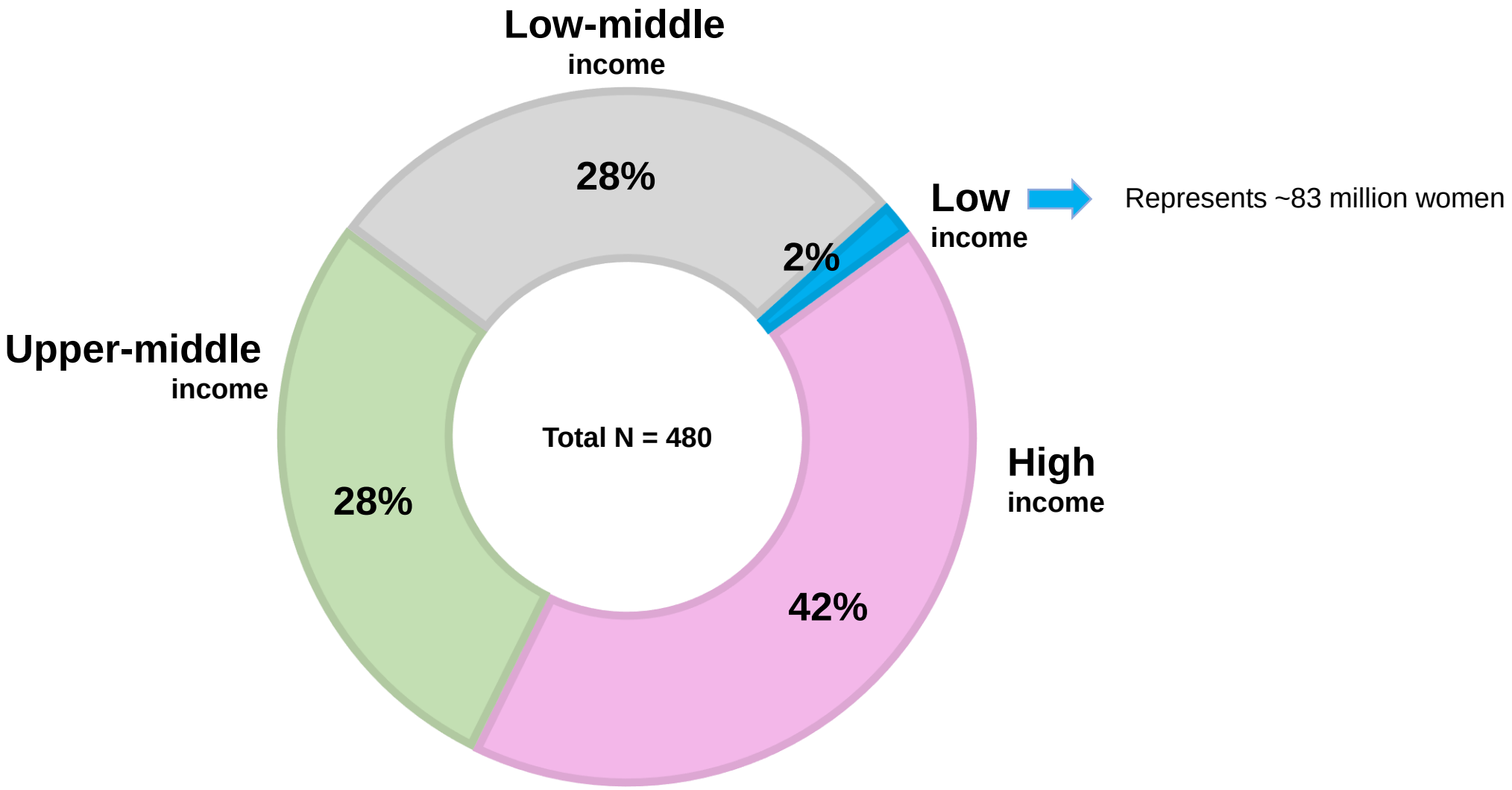
Distribution of Survey Participants

Using 2023 WHO-defined country names

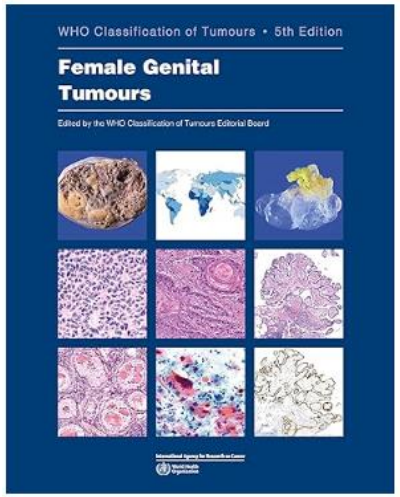
USA	65
India	50
Turkey	35
Egypt	32
Brazil	28
Philippines	26
UK	23
Canada	15
Romania	15
Spain	13
Russian Federation	11
Australia	8
China	8
Mexico	8
Ethiopia	6
Peru	6
South Africa	5
United Arab Emirates	5
Argentina	4
Armenia	4
France	4
Italy	4
Japan	4
Malaysia	4
Netherlands	4
Pakistan	4
Portugal	4
Sri Lanka	4
Azerbaijan	3
Belgium	3
Chile	3
Ecuador	3
Germany	3
New Zealand	3
Republic of Moldova	3
Sweden	3
Viet Nam	3
Zambia	3
Colombia	2
Czechia	2
El Salvador	2
Finland	2
Ghana	2
Indonesia	2
Ireland	2
Nigeria	2
Norway	2
Oman	2
Republic of Korea	2
Thailand	2
Venezuela	2
Algeria	1
Austria	1
Bahamas	1
Bahrain	1
Belarus	1
Brunei Darussalam	1
Fiji	1
Greece	1
Hungary	1
Iran	1
Iraq	1
Kenya	1
Morocco	1
Myanmar	1
Nepal	1
North Macedonia	1
Rwanda	1
Saudi Arabia	1
Serbia	1
Switzerland	1
Tunisia	1
Ukraine	1
United Republic of Tanzania	1
Uruguay	1
Yemen	1

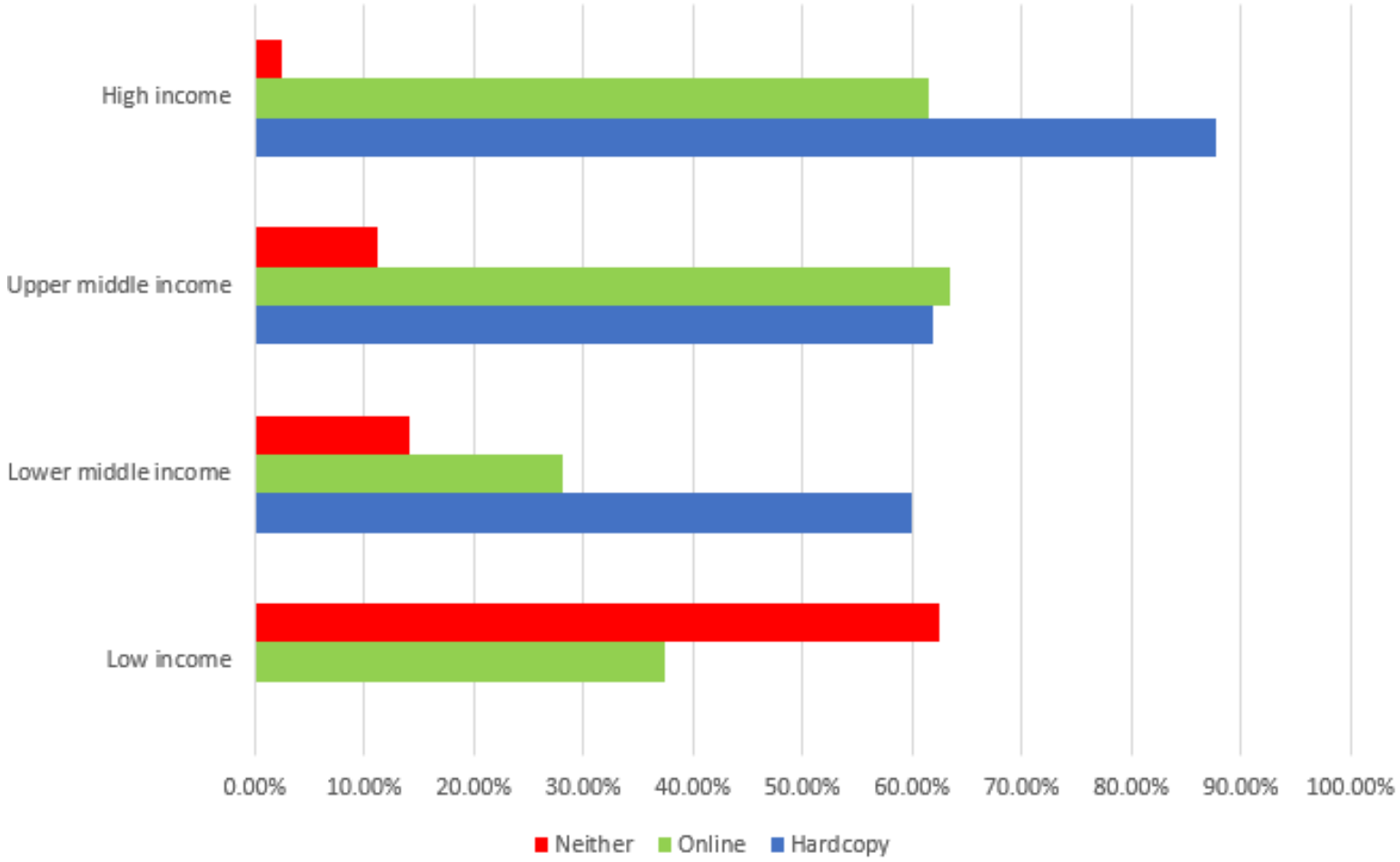
Distribution of Survey Participants

Country Economic Category

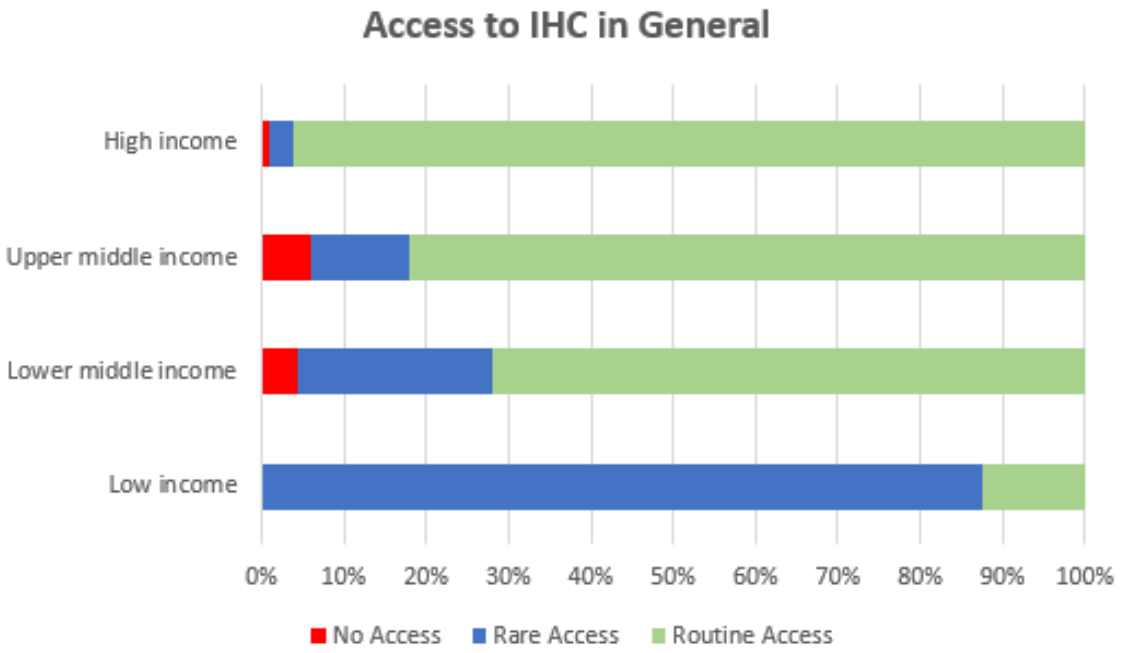


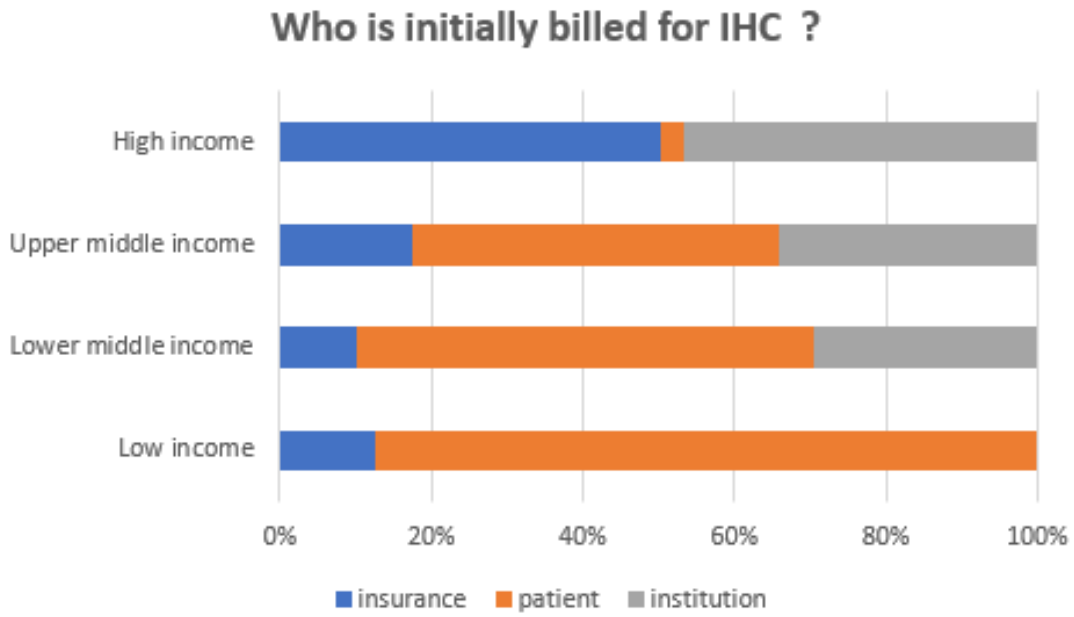
Access to WHO “Blue Book” for Female Genital Tumors





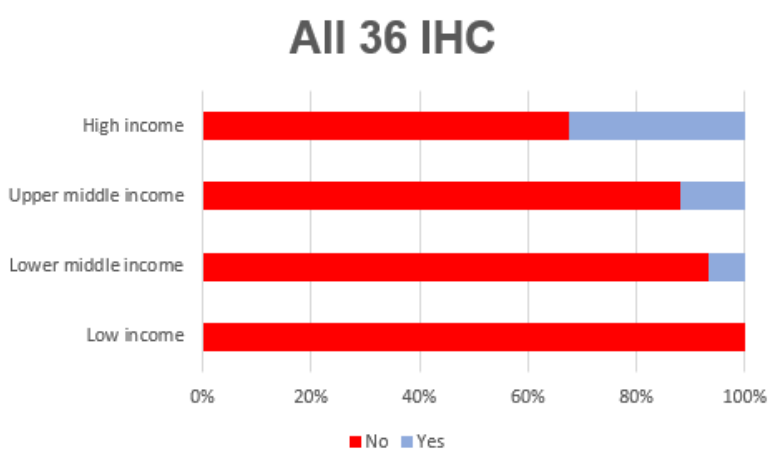
General Access to IHC and Billing

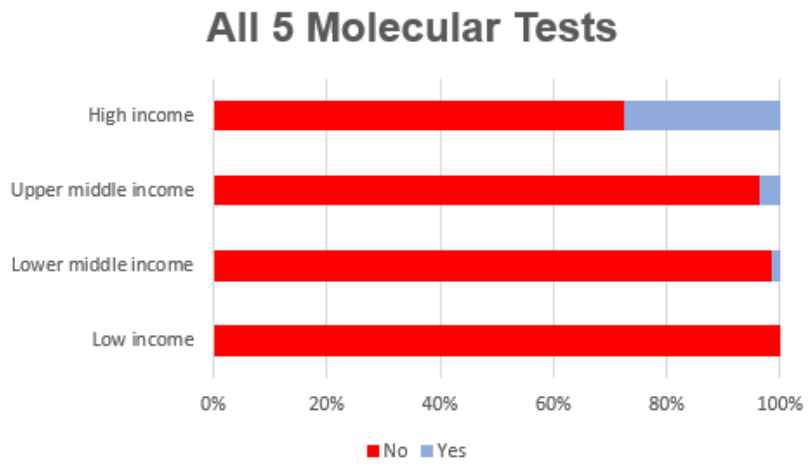


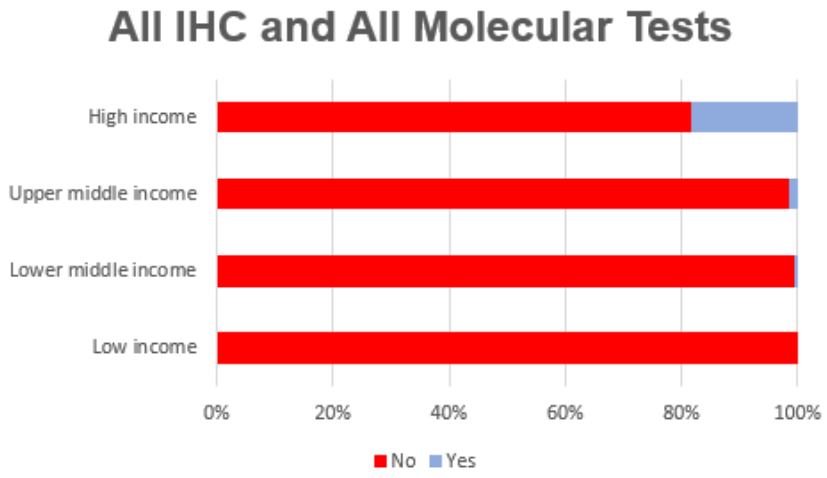


Respondents with Routine Access to All of the Required Tests

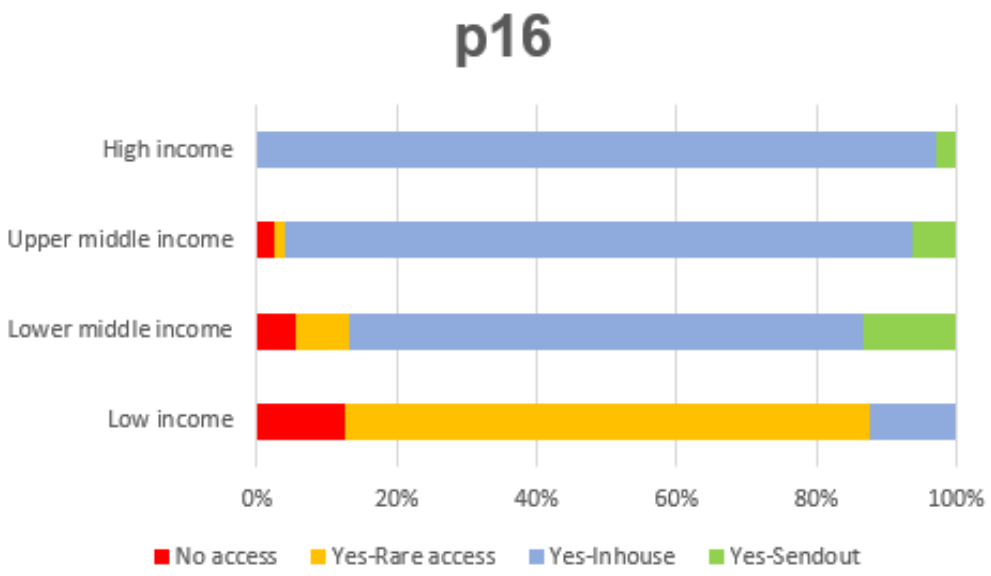
Inhouse or send-out access

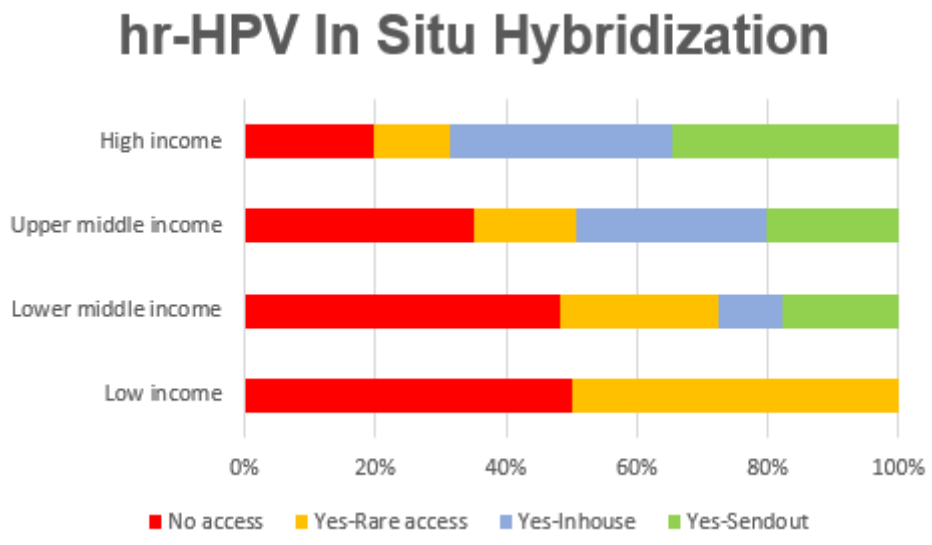




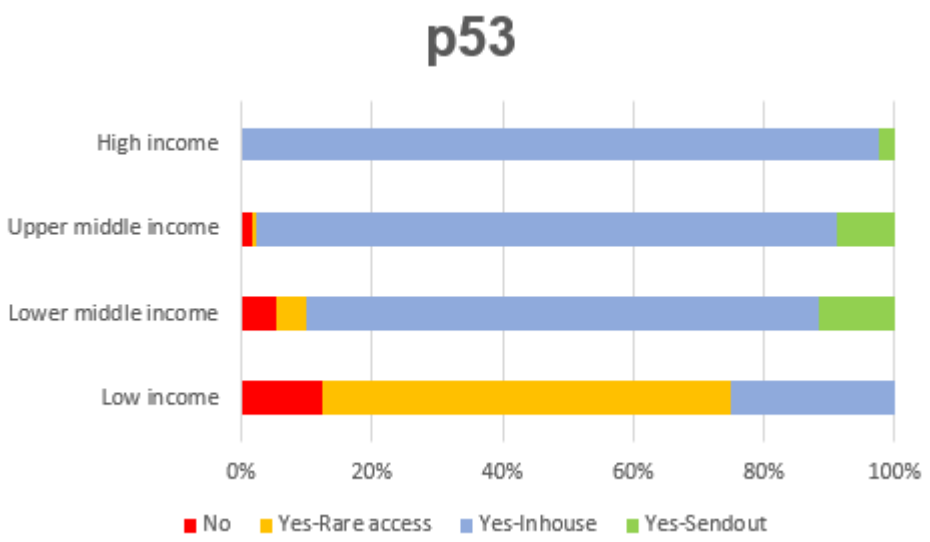


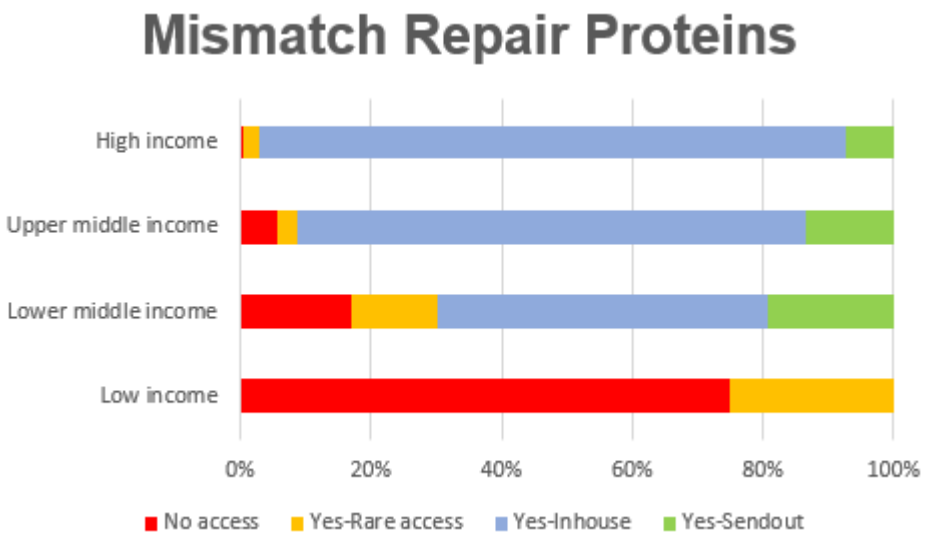
High Risk HPV-associated Tests

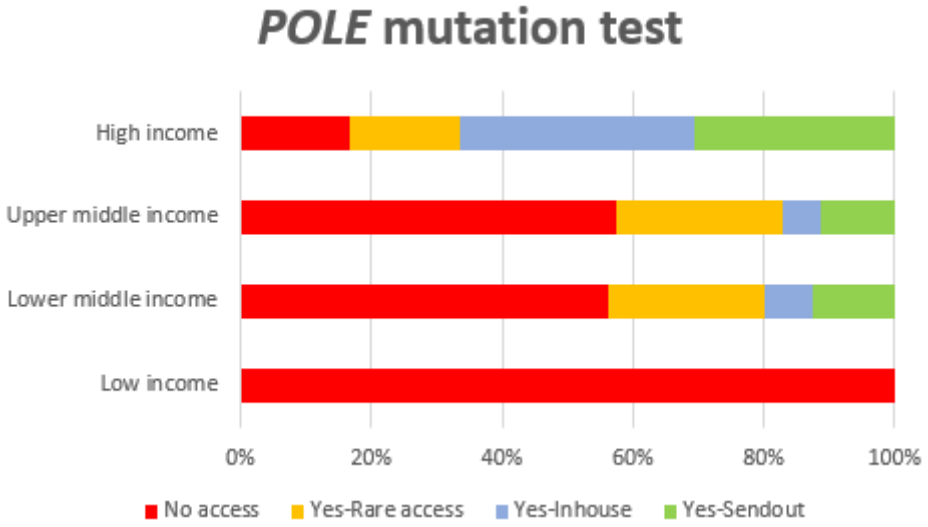




Endometrial Cancer-related Tests

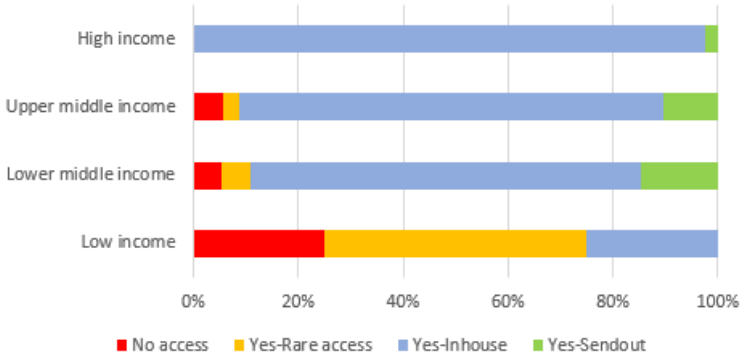




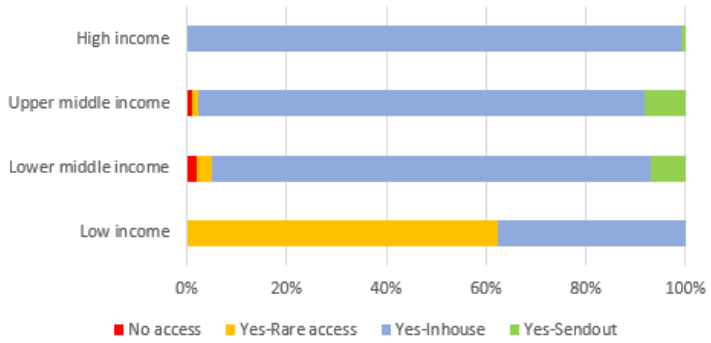


Ovarian Tumor-related Markers

WT1

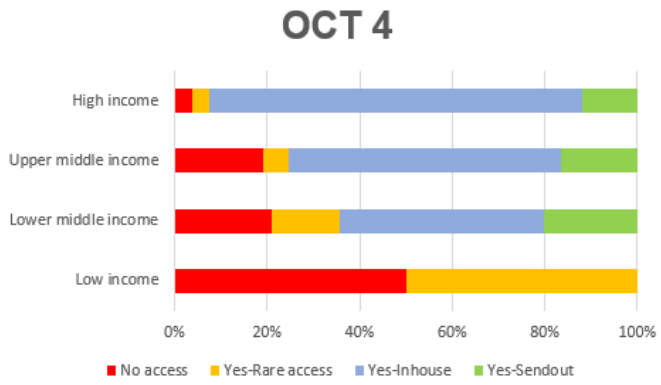


Estrogen Receptor



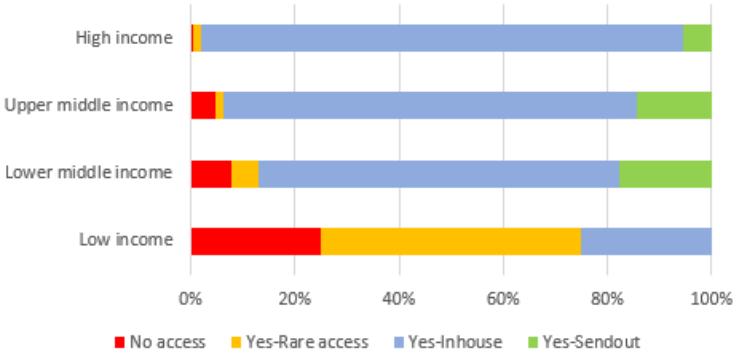
Germ Cell Markers

OCT 4

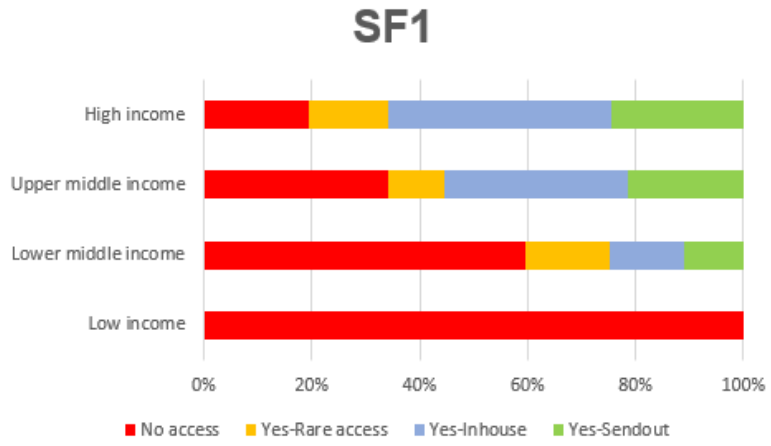


Sex Cord-Stromal Markers

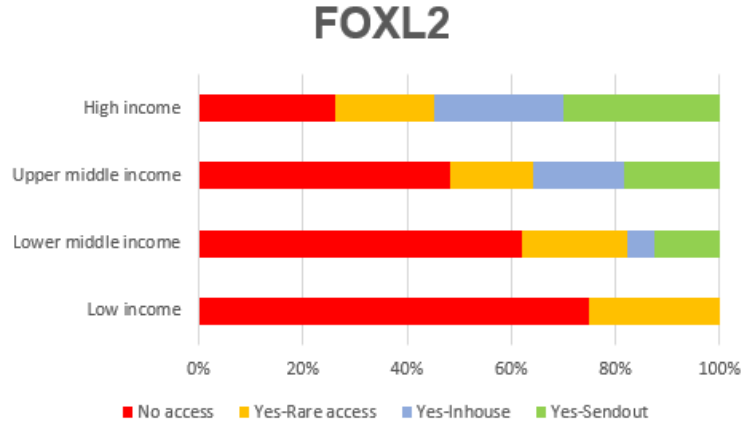
Inhibin



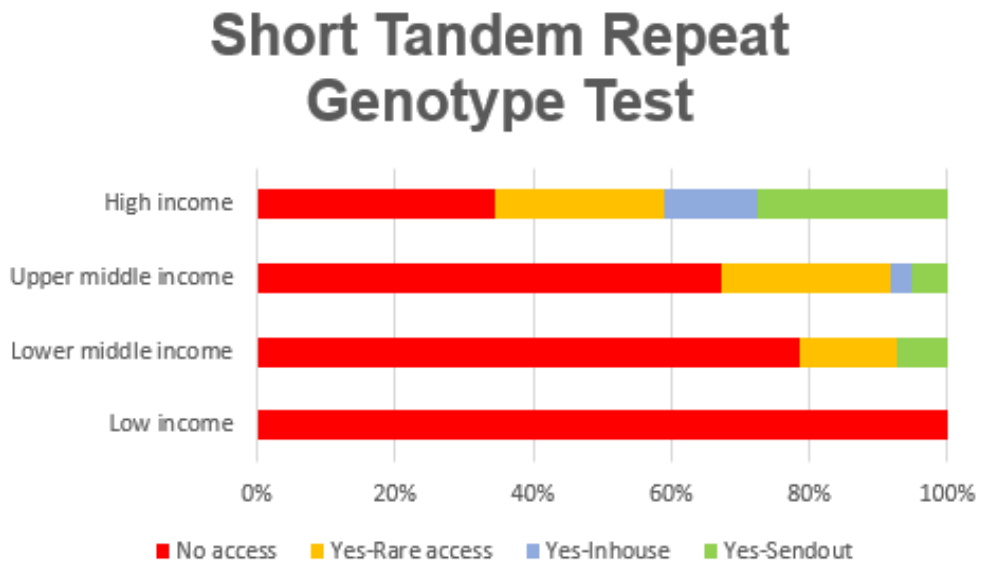
SF1



FOXL2

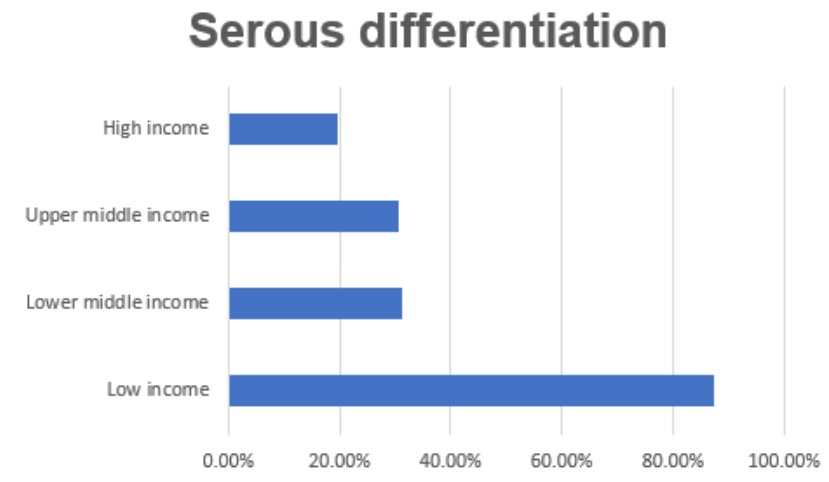


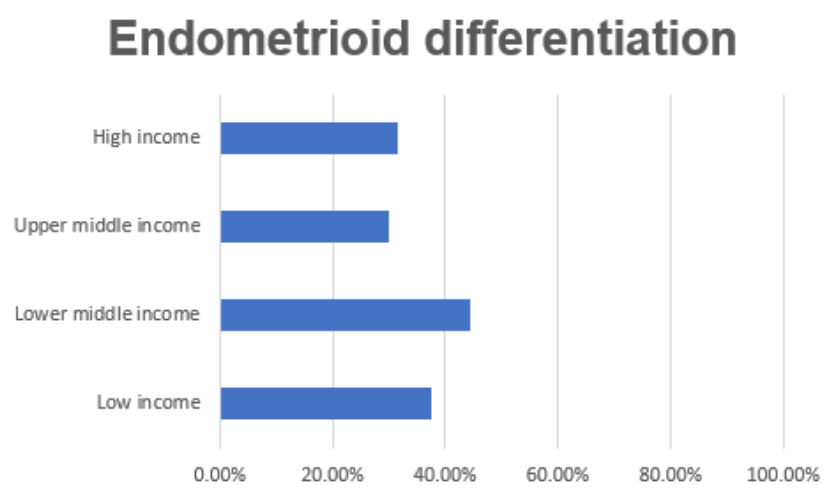
Molar Pregnancy Test

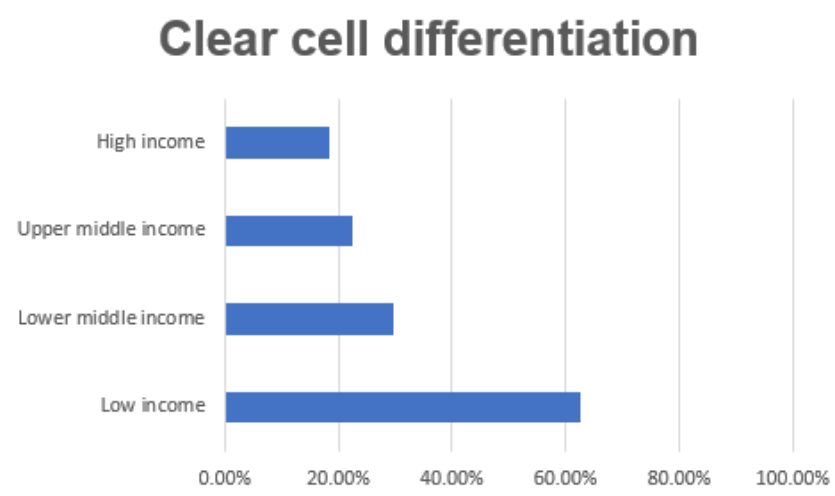


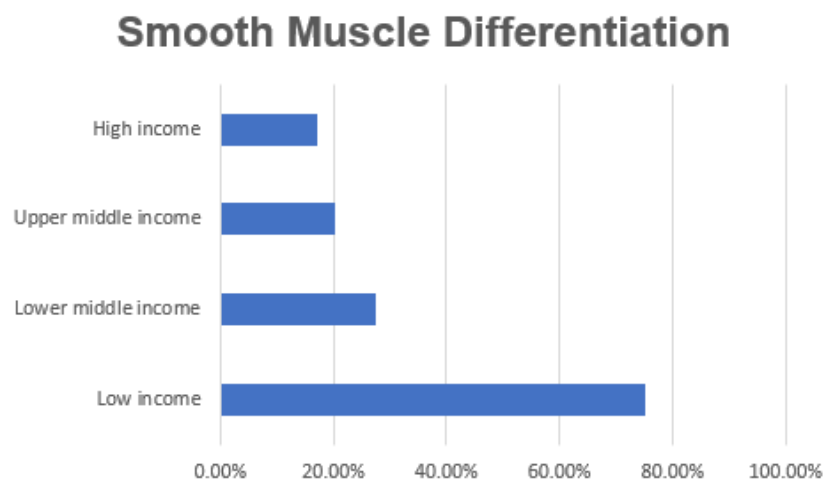
Practice of Routinely Diagnosing without IHC

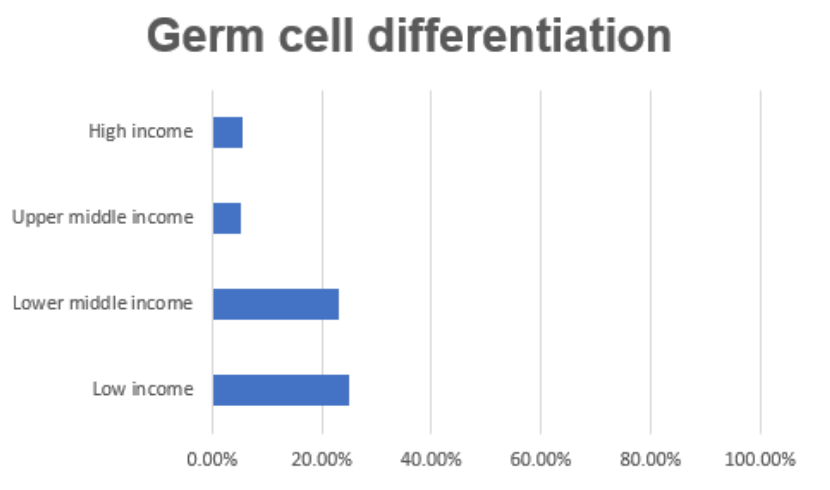
An Uncommon Practice

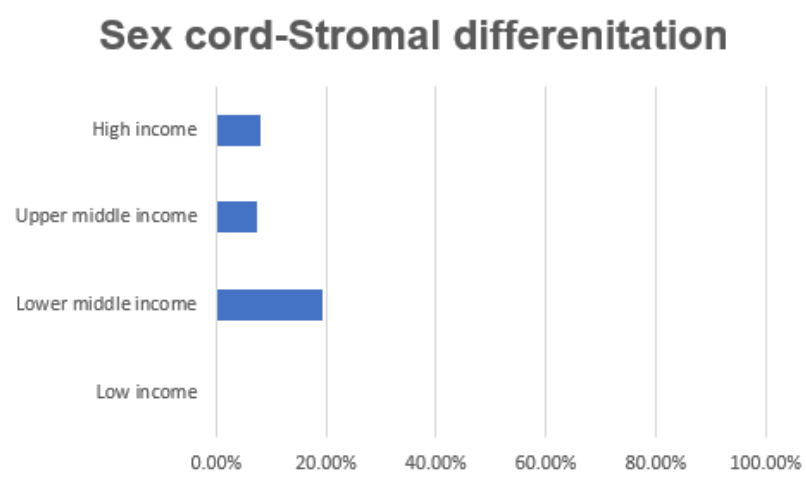












Study Limitations

- **English-only survey**
- **Sample size is small**
- **Recruitment biased towards sub-specialists**
- **Low income countries not well represented**
- **World Bank economic categories are imperfect**
- **Economic status not evaluated at the level of the institution/practice**

- **Need for a WHO “compliant” diagnosis is not universal but varies by local environment**
  - *Best practices for patient care are locally defined*

Conclusions

1. **Some WHO “essential criteria” may be challenging to meet**

   - Requirement for access to a large array of IHC and molecular tests
   - Scale of the requirement is under-appreciated due to many “essential criteria” that indirectly require IHC to establish “differentiation”

2. **Lower economic environment is associated with:**

   - Lower access to WHO “blue books”
   - Lower access to “essential” IHC / molecular tests
   - Higher burden on patients to pay for IHC

   } *Health care disparity*

Potential Next Steps

Starting a conversation

- **Standardize the goal of WHO "essential criteria"**
  - define criteria for when WHO authors should include IHC / molecular tests as "essential"

- **Offer optional detailed "morphology-only" based WHO "essential criteria"**
  - as a parallel option for use in resource-constrained environments
  - need stakeholder engagement of local pathologists / clinicians

- **Develop pathways to make the WHO "blue book" accessible to <u>all</u> pathologists**
  - regardless of their economic environment