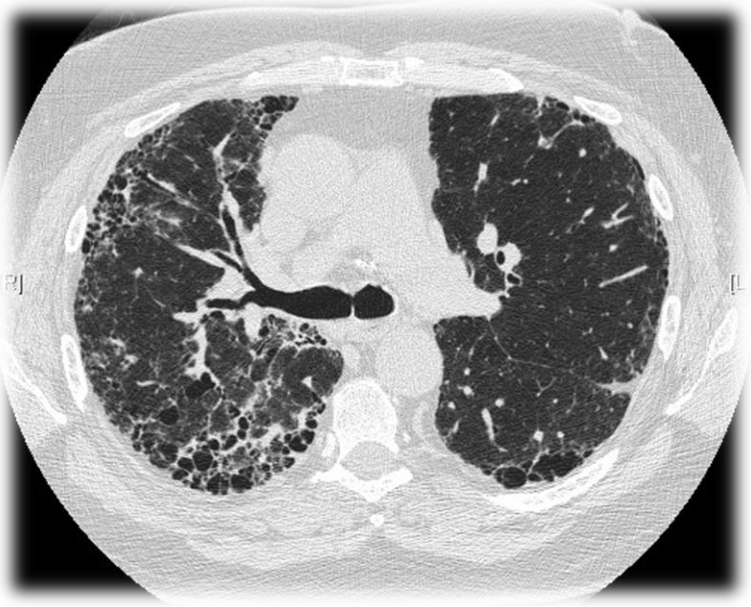
IDIOPATHIC PULMONARY FIBROSIS

…..LIMITS TO CARE, INCLUDING LIMITS TO ACCESSING SPECIALISTS, LIMITS AND STOPPING RULES FOR DRUGS, OXYGEN AND OTHER THERAPEUTIC REGIMENS

….HOW WE CAN MAKE WHAT PATIENTS 'VALUE' WORK IN THE CONTEXT OF FISCAL RESTRAINT



Toronto, April 2016

McMaster University

FIRH Firestone Institute for Respiratory Health

St. Joseph's Healthcare Hamilton

Martin Kolb *MD, PhD*

Division Director Respirology

Research Director Firestone

Presenter Disclosures

Martin R.J. Kolb

Financial relationships with commercial interests relevant to this presentation:

Professional Fees paid to me:

- Member of Advisory Boards or consultant for Boehringer Ingelheim, GSK, Roche-Intermune, Gilead, Janssen, Genoa, Prometic
- Member of Boehringer Ingelheim Steering Committee for INPULSIS
- Speaker honoraria from Boehringer Ingelheim, Roche-Intermune, AZ

Paid to my institution:

- Principal Investigator for IPF trials (Boehringer Ingelheim, Centocor, Intermune, Roche, Sanofi, Gilead)
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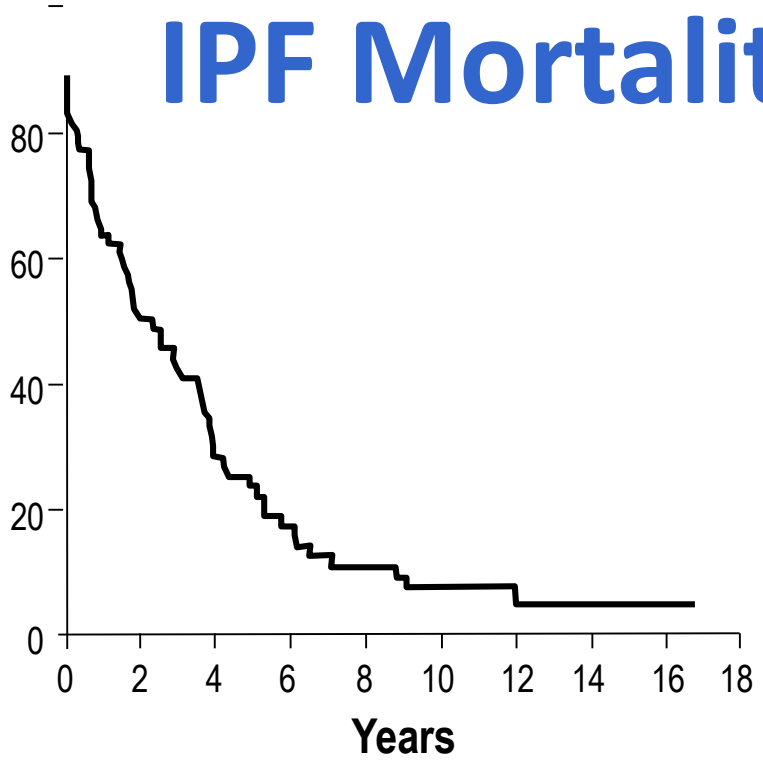
- Educational Grants from Roche-Intermune

Epidemiology and Survival of IPF from National Data in Canada

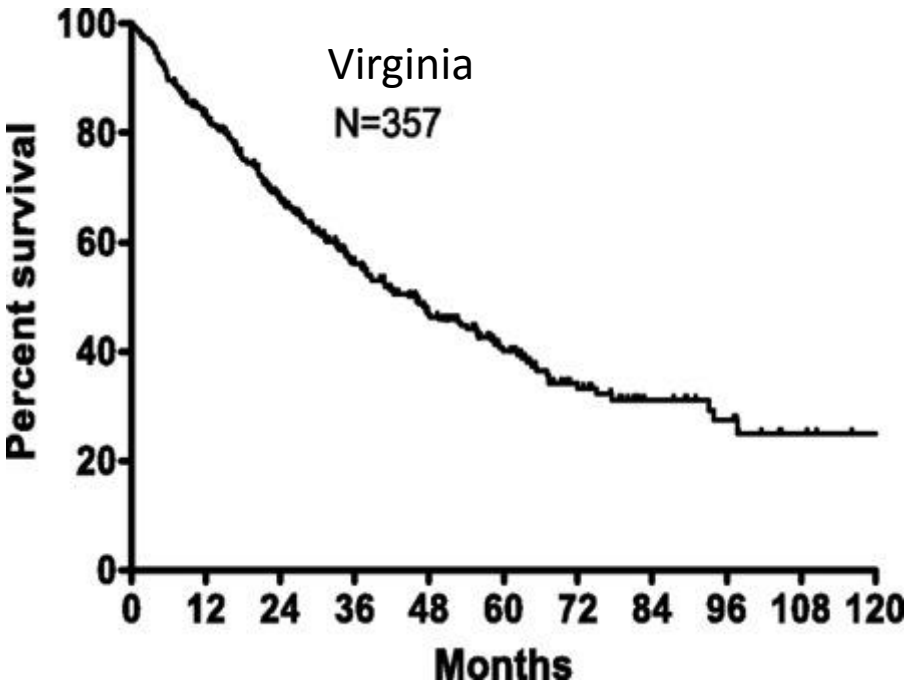
First author	Country	Source	Study period	Age (yrs)	Cases (n)	Prevalence per 100,000	Incidence per 100,000	Projected Canadian Prevalence per 100,000	Projected Canadian Incidence per 100,000
Fernandez Perez(1)	USA	Community cohort	1997-2005	50+	47	63.0 (B) 27.8 (N)	17.3 (B) 8.8 (N)	7,352 (B) 3,244 (N)	2,019 (B) 1,781 (N)
Gribbin(2)	UK	THIN GP data (255 GP) (3% pop)	1991-2003	40+	920		4.6		776
Navaratnam(3)	UK	THIN GP data (446 GP)	2000-2009	40+	2,074		7.44		1,255
Coultas(4)	USA	ILD autopsies, community cohort	1988-1990	18+	510	20.2 Men 13.2 Women	10.7 Men 7.4 Women	4,357	2,378
Raghu(5)	USA	Health care claims (<1% pop)	1996-2000	18+	1,943 (Prev) 387 (Inc)	42.7 (B) 14.0 (N)	16.3 (B) 6.8 (N)	11,183 (B) 3,666 (N)	4,269 (B) 1,781 (N)
Lai(6)	Taiwan	National health insurance (11% pop)	1997-2007	18+	418	6.4 (B) 4.9 (N)	1.4 (B) 1.2 (N)	1,676 (B) 1,283 (N)	367 (B) 314 (N)
Von Plessen(7)	Norway	Hospital records (5% pop)	1984-1998	16+	158 (CFA)	23.4	4.3	6,128	1,126
Hodgson(8)	Finland	National pulmonary clinics	1997-1998	All	1,445	18		6,140	
Karakatsani(9)	Greece	Survey of pulmonologists	2004	All	189 (Prev) 52 (Inc)	3.38	0.93	1,153	317
Kolek(10)	Czech Republic	24 centre study	1981-1990	All	488 (CFA)	12.1	0.94	4,127	321
Kornum(11)	Denmark	National admission data (100% pop)	1995-1998	All	1,417	5.28	2.91	1,801	993
Thomeer(12)	Belgium	ILD registry (57% pop)	1992-1996	All	72	1.25	0.22	426	75
Xaubet(13)	Spain	Survey of pulmonologists	2000-2001	All	197 (Inc)		2.94		1,003
Hopkins	Canada	National data admissions (100% pop); emergency/day surgery (50% pop)	2011	All	12,268	41.8 (B) 20.0 (N)	18.7 (B) 9.0 (N)	14,259 (B) 6,822 (N)	6,390 (B) 3,057 (N)

Hopkins R & Kolb M; Eur Resp J 2016

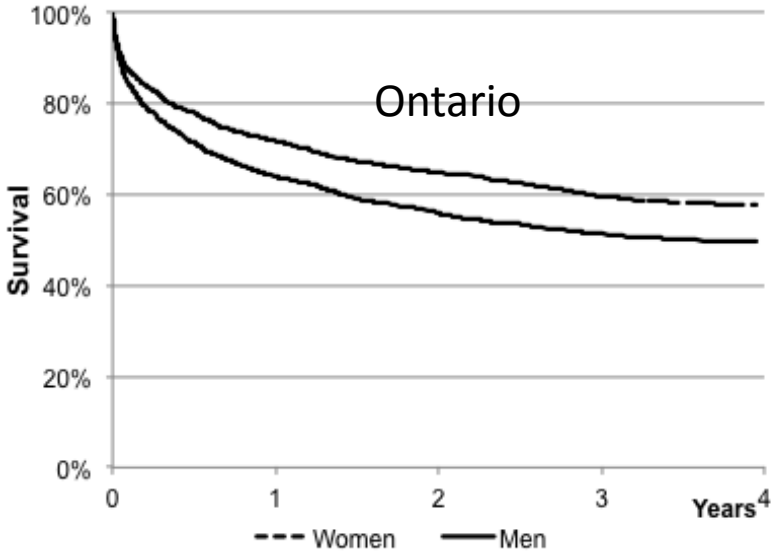
IPF Mortality



Bjoraker JA et al, AJRCCM 1998



Nathan SD et al, Chest 2011



3-4 yr ≈ 50% death rate

Hopkins R & Kolb M; ERJ 2016

IPF – Access to Specialists in Canada

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- Long wait lists
- Referral often too late
- Referral sometimes too unselective
- Time consuming consultations
- Limited resources for specialty clinics

IPF – Access to Therapy in Canada

- Oxygen
- Specific rehabilitation programs
- Palliative Care
- Lung transplantation
- Pirfenidone
- Nintedanib

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The Walking Winded: Oxygen in Pulmonary Fibrosis

Kerri A. Johannson, Sachin R. Pendharkar, Kirk Mathison, Charlene D. Fell, Jordan A. Guenette, Meena Kalluri, Martin Kolb, Christopher J. Ryerson

(manuscript under review)

Jurisdiction	**Resting Criteria***	**Exertional Criteria**
British Columbia	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	• SpO_2 < 88% and increased walk distance by > 25% and 30m • SpO_2 < 80%
Alberta	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	• SpO_2 < 80% • Decreased dyspnea • Increased walk distance by 30m and 25%
Saskatchewan	• PaO_2 < 60mmHg or SpO_2 < 87% with comorbidity • PaO_2 < 55mmHg or SpO_2 < 90%	• SpO_2 < 88% and increased walk distance by ≥ 20%
Manitoba	• PaO_2 < 60mmHg	• SpO_2 < 90% and increased walk distance by > 25% and 30m
Ontario	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	• SpO_2 < 80% • SpO_2 < 89% and increased walk distance by HOW MUCH?
Quebec	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	No funding
New Brunswick	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	• SpO_2 < 89%
Nova Scotia	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg • SpO_2 < 89%	• SpO_2 < 80%
Prince Edward Island	• PaO_2 < 60mmHg with comorbidity • PaO_2 < 55mmHg	No funding
Newfoundland	No funding	No funding

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CDEC FINAL RECOMMENDATION

PIRFENIDONE RESUBMISSION
(Esbriet — Hoffmann-La Roche Limited)
Indication: Idiopathic Pulmonary Fibrosis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that pirfenidone be listed for the treatment of adults with mild to moderate idiopathic pulmonary fibrosis (IPF), if the following clinical criteria and conditions are met:

Criteria:
- Mild to moderate IPF, defined as forced vital capacity (FVC) greater than or equal to 50% of predicted
- Stable disease, defined as FVC not decreased by ≥ 10% during the previous 12 months
- Treatment discontinued if FVC declines by ≥ 10% within any 12-month period while receiving therapy

Conditions:
- Patient is under the care of a specialist with experience in the diagnosis and management of patients with IPF
- Substantial price reduction

CDEC Meeting — February 18, 2015; CDEC Reconsideration — April 8, 2015
Notice of Final Recommendation — April 15, 2015

Other Discussion Points:
CDEC noted the following:

- Pirfenidone has a Health Canada indication for the treatment of mild to moderate IPF in adults; however, CDEC noted that there is the potential for broader use outside the scope of the approved indication (e.g., severe IPF).
- CDEC noted that the listing criteria for pirfenidone currently used by many of the CDR-participating drug plans requires both of the following as part of the diagnosis for mild to moderate IPF: FVC between 50% to 80% predicted and the per cent of diffusing capacity for carbon monoxide (DLCO) between 30% and 90% predicted. CDEC considered these criteria and noted that challenges with the application and analysis of the DLCO limit its utility in evaluating the severity of IPF.
- At the recommended dose, patients are required to take three capsules, three times daily (total of nine capsules daily). Although, this is a large pill burden, CDEC noted that patients with mild to moderate IPF are likely to be compliant given the severity of this condition.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the longer term efficacy and safety of pirfenidone.

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CADTH CDEC FINAL RECOMMENDATION

NINTEDANIB
(Ofev — Boehringer Ingelheim Canada Ltd.)
Indication: Idiopathic Pulmonary Fibrosis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that nintedanib be listed for the treatment of idiopathic pulmonary fibrosis (IPF), if the following clinical criteria and conditions are met:

Clinical Criteria:

- Forced vital capacity (FVC) greater than or equal to 50% of predicted.
- Treatment with nintedanib should be discontinued if absolute FVC declines by ≥ 10% within any 12-month period while receiving therapy.

Conditions:

- Under the care of a specialist with experience in the diagnosis and management of IPF.
- Drug plan cost for nintedanib must not exceed the drug plan cost for pirfenidone.

CDEC Meeting — September 16, 2015
Notice of Final Recommendation — October 15, 2015

Other Discussion Points:

CDEC noted the following:

- Nintedanib and pirfenidone have different mechanisms of action; however, there is no evidence evaluating the efficacy and safety of their combined usage. There is potential for these two products to be used in combination, which could be associated with significant costs for the CDR-participating drug plans.
- Two indirect comparisons suggested similar efficacy between nintedanib and pirfenidone; however, due to heterogeneity across the included RCTs, CDEC concluded that there remains uncertainty regarding the comparative safety and efficacy for these two treatments.
- The two INPULSIS trials did not exclude people with normal lung function, while the ASCEND trial comparing pirfenidone against placebo imposed an upper limit on FVC. This resulted in a clinically meaningful difference in baseline per cent predicted FVC between the INPULSIS and ASCEND trials and suggested that patients in ASCEND may have had more advanced disease. This difference in baseline disease severity may have influenced the number of mortality events in the trials and impacted the ability to observe a mortality benefit with nintedanib.
- The twice-daily dosing schedule for nintedanib is more convenient than the dosing schedule for pirfenidone (i.e., three capsules taken three times daily).
- CDEC noted that patients who are intolerant to pirfenidone could be considered for treatment with nintedanib.

At the recommended daily dose of nintedanib (150 mg twice daily), nintedanib ($109 per day) is less costly than pirfenidone ($117 per day); therefore, when comparing only drug costs, treatment with nintedanib results in modest cost savings compared with pirfenidone.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no studies directly comparing nintedanib against pirfenidone for the treatment of patients with IPF.
- There is no evidence addressing the use of nintedanib in patients who have failed treatment with pirfenidone.

Requirements for all New Esbriet or Ofev prescriptions

1. **PFT done within 3 months of prescription** – must be interpreted and meet ATS standards (criteria is **"mild to moderate IPF", FVC 50-80% pred, DLCO 30-90% pred**)
2. **HRCT done in the last 24 months** (no contrast) – interpretation must **specifically state that UIP pattern is observed**. If the interpretation describes differential diagnosis or diagnosis is unclear and requires clinical correlation then the dictated follow up letter must address this to clarify the clinical features which lead you to the diagnosis of IPF.
3. **Clinical letter (day of prescription)** – should include a summary detailing how IPF was clinically confirmed whereby ALL other forms of interstitial lung disease (including environmental exposure, medication or systemic disease) have been investigated and excluded in this patient. Also should include additional information regarding HRCT scan interpretation if necessary (see above).

“INSPIRATION” (Esbriet)

EAP form and Inspiration program enrolment form are to be completed. Each will need to be signed by the ordering physician. All of the documentation (PFT, HRCT report, clinical letters) will be forwarded to the program and they will then review and send to the Ministry.

As we are trying to minimize the number of patients who start drug on a bridging basis while awaiting EAP approval who **do not** meet the EAP criteria, it is necessary to explain to the patient that **the process may take about 4 weeks**. Once the program and/or EAP have determined eligibility, drug will be shipped and the patient will start. Patients who do not meet the EAP criteria because of PFT results will be started on a compassionate basis without having to wait for EAP decision.

RENEWAL

Patients are currently required to have a pulmonary function test done 12 months after starting Esbriet to **demonstrate that they have NOT had progression of disease defined by an absolute decline in percent predicated FVC of 10% or greater from initiation** of therapy. If a progression is documented, a repeat PFT can be done 4 weeks later for confirmation. This report must be submitted with an EAP form documenting the renewal application for funding. (**Spirometry will not be accepted**.)

Request for Reimbursement of Esbriet® (Pirfenidone) - Exceptional Access Program* (EAP)

Please ensure that all appropriate information for each section is provided to avoid delays and fax the completed form and/or any additional information to 416-327-7526 or toll-free 1-866-811-9908; or send to Exceptional Access Program Branch (EAPB), 3rd floor, 5700 Yonge Street, Toronto ON M2M 4K5.

SECTION 1 – Prescriber Information

First name	Initial	Last name
Martin		Kolb

Street no.	Street name
50	Charlton Ave E

City	Postal code
Hamilton	L8N 4A6

Fax no.	Telephone no.
(905) 521-6183	(905) 522-1155 x34144

SECTION 2 – Patient Information

First name	Initial	Last name

Ontario Health Insurance Program Number

Date of birth (yyyy/mm/dd)

SECTION 3 – Drug Requested

Esbriet® (pirfenidone) 267 mg capsules DIN 02393751
*Refer to product monograph for dosing guidelines

☐ Initial request **(Complete Section 4)**

☐ Renewal request **(Complete Section 5)**
EAP request #_____

SECTION 4 – Clinical Information

1. **Requesting Physician**
   - i) Is a respirologist: ☐ Yes ☐ No (Specialty: _____)
   - ii) Is experienced in the diagnosis and management of IPF: ☐ Yes ☐ No
   - iii) Is the diagnosing respirologist: ☐ Yes ☐ No (Name of respirologist: _____)

2. **Esbriet Funding**
   - **i)** For treatment of: ☐ IPF ☐ Other (Specify diagnosis:_____)
   - **ii)** Patient has started Esbriet (via Inspiration Program/manufacturer, third party payors, clinical trials, physician's samples, out of pocket expenses, etc.): ☐ Yes (Specify actual start date: _____ yyyy/mm/dd) ☐ No

3. **Confirmation of Diagnosis – ATTACH COPIES OF DIAGNOSTIC REPORTS INCLUDING THE INTERPRETATION SECTIONS**
   - **i)** ☐ High Resolution Computerized Tomography (HRCT) scan **attach copy of initial HRCT scan report* (Date_____ yyyy/mm/dd)
   - **ii)** ☐ Lung Biopsy [if HRCT scan not definitive for IPF, and performed] **attach copy of biopsy report* (Date_____ yyyy/mm/dd)
   - **iii)** ☐ Clinical confirmation whereby ALL other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medication or systemic disease (connective tissue/collagen vascular) have been investigated and excluded.* (Date_____ yyyy/mm/dd)

   ***PHYSICIAN IS ENCOURAGED TO ATTACH A BRIEF SUMMARY DETAILING HOW IPF WAS CLINICALLY CONFIRMED IN THIS PATIENT (Maximum: One Page). A detailed consult note from an ILD clinic confirming IPF may be provided in lieu, if applicable.**

4. **Pulmonary Function Tests (PFTs) – ATTACH COPIES OF RELEVANT PFT REPORTS BELOW**

   ☐ Treatment naïve to Esbriet:
   Most recent PFTs (with FVC and uncorrected DLCO values as % predicted) **performed within 3 months of current date**: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)

   ☐ Treatment experienced to Esbriet:
   - i) Last PFTs (with FVC and uncorrected DLCO values as % predicted) **performed within 3 months PRIOR to actual start date of Esbriet**: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)
   - ii) If patient has been **on Esbriet for at least six (6) months**, specify date of most recent /current PFTs (with FVC value as % predicted) performed while on Esbriet: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)

SECTION 5 – Renewal Information

Refer to most recent funding approval letter for timing of on Esbriet PFTs - ATTACH COPIES OF ALL PFT REPORTS BELOW

- i) Date of actual Esbriet initiation: (Date_____ yyyy/mm/dd)
- ii) Date of last pre-Esbriet PFTs performed: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)
- iii) Date of most recent PFTs (FVC as % predicted) performed while on Esbriet: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)
- iv) Date of confirmatory PFTs (FVC as % predicted) conducted 4 weeks later if there is an absolute decline in the percent predicted FVC of at least 10% since initiation of Esbriet: **PFT report MUST be provided* (Date_____ yyyy/mm/dd)

Physician signature (*mandatory*)	CPSO Number	Date

EAP application form for Esbriet in Ontario

“HEADSTART” (Ofev)

In the anticipation of funding approval for Ofev, we will probably be required to go back and provide the same information to EAP for funding as we currently do for Esbriet. Patients currently receive drug on a compassionate basis very quickly from Headstart.

We try to ensure that we met the same requirements so that it will be a relatively smooth transition to apply to EAP for patients receiving treatment.

Hurdles of drug access from the EAP, Ontario

Examples from EAP notifications:

"Patients must NOT demonstrate progression of disease defined as an absolute decline in the percent predicted FVC of 10% or greater since initiation of therapy (baseline). If a patient has experienced progression as defined above, the results should be validated with a confirmatory pulmonary function test conducted 4 weeks later.

The above guidelines remain applicable in cases where EAP coverage is required to provide continued treatment that was previously supplied through a clinical trial or paid for by other means such as third party payers."

- Some patients have been on treatment since 2013 through third party payers or in open label clinical trials for a number of years and as such, a 10% decline in FVC may be observed since baseline but due to the length of time on treatment, the drug could very likely have preserved the fall to which the FVC may have declined without therapy. These patients would be declined funding.

Hurdles of drug access from the EAP, Ontario

Examples from EAP notifications:

"Please discuss whether the diagnosis of IPF has been clinically confirmed including whether other etiologies such as arthritis, collagen vascular or connective tissue disease (scleroderma), occupational/environmental inhalations and medication exposures, etc, have been investigated and excluded in this patient. "

"The physician is strongly encouraged to attach a brief summary detailing how IPF was clinically confirmed in this patient (maximum one page). A detailed consult note from an ILD clinic confirming IPF may be provided in lieu, if applicable."

- **80% of submissions are returned to the clinical site** as a Request for Additional Information with the above question. All EAP submissions include a pre-Esbriet PFT, CT scan report and a copy of the clinical note from the patient's chart (usually consult or diagnosing visit letter and letter from most recent clinical visit). This request has also been sent when biopsy results accompany the submission.
- Clarification is also requested, even if all clinical data (including clinical letter/summary) is sent with application, when a HRCT scan report states "**possibility of mild pulmonary fibrosis, UIP type but other possibilities are within the differential. Clinical correlation necessary.**"

Hurdles of drug access from the EAP, Ontario

- **FVC 50-80% predicted and DLCO 30-90%**
  - **This does not take into consideration the predicted set that different centers use**
    - For example, with our FRCAU predicted set a patient had a DLCO 22% predicted but when results 3 months later were received from UHN (using CDN-UHN predicted set) the DLCO was reported as 30% (yet the observed values were 5.0 and 5.2 respectively, which does not account solely for the difference). Patient met criteria and was funded but after multiple submissions.
  - **Patients with an FVC predicted greater than 80% are not funded – as this is a value generated from a predicted set and those who are not ideally suited to the predicted set are penalized.**
    - For example: Caucasian Female, Height 151 cm, age 74 years – FVC predicted value 2.31 L, FVC pre 2.10 L, percent predicted 91%; DLCO 25% predicted. Biopsy proven IPF/UIP and clinical correlation relates to disease. Ministry not funding Esbriet, treated through compassionate program since Feb 2015.

Hurdles of drug access from the EAP, Ontario

- **Criteria for initial consideration for funding are a reported pulmonary function test including FVC and DLCO. Once approval for funding is granted, PFT's are requested every six months (or in some cases, funding is given for a shorter time, 1-4 months). Since the predicted FVC is the only value being compared at renewals, spirometry reports should be accepted from accredited pulmonary function labs. Spirometry reports could be provided from accredited centers.**
  - **The benefits of accepting spirometry reports from accredited centers include:**
    - Reduced cost to the Healthcare System by performing spirometry as opposed to full pulmonary function tests
    - Shorter wait times for all patients as pulmonary function labs can have wait times of 4-6 weeks depending on the center
    - Less stress and physical burden to patients with IPF who would not have to perform the PFT if not clinically necessary. Shortness of breath, light-headedness, fatigue and headache are frequently reported post pulmonary function testing

Hurdles of drug access from the EAP, Ontario

- **Every 6 month renewal must also include a copy of the pre-Esbriet PFT which was sent with initial submission. Additional paperwork to complete EAP renewal form and pull all testing since drug start.**

- **Patients who received funding from private insurers prior to the initiation of the ministry funding program may not have Esbriet-naïve testing within the time window the ministry requires. They are then denied funding after receiving Esbriet through their insurer since we cannot turn back the clock to provide PFT's within 3 months of drug start if it wasn't done at the time. Moving forward we are trying to ensure ministry requirements are met (PFT's and HRCT's available) prior to private insurer's coverage.**

Hurdles of drug access from the EAP, Ontario

Lately, we have been receiving more notice of approvals than denials and the response time of the ministry has improved since funding was initiated!

It is imperative that all testing is collected and all forms are completed for EAP prior to enrolling and dispensing drug through Inspiration program – otherwise, if something is missing or needs to be repeated and the patient has started drug, we can no longer provide Esbriet-naïve results.

For a busy ILD clinic with multiple (2-3) respirologists, the time to coordinate access to drug is a very big undertaking, addressing ministry, program and patient concerns daily.