Inclusion of Protons in Large Scale Clinical Trials – US Approach

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AAPM, July 2022

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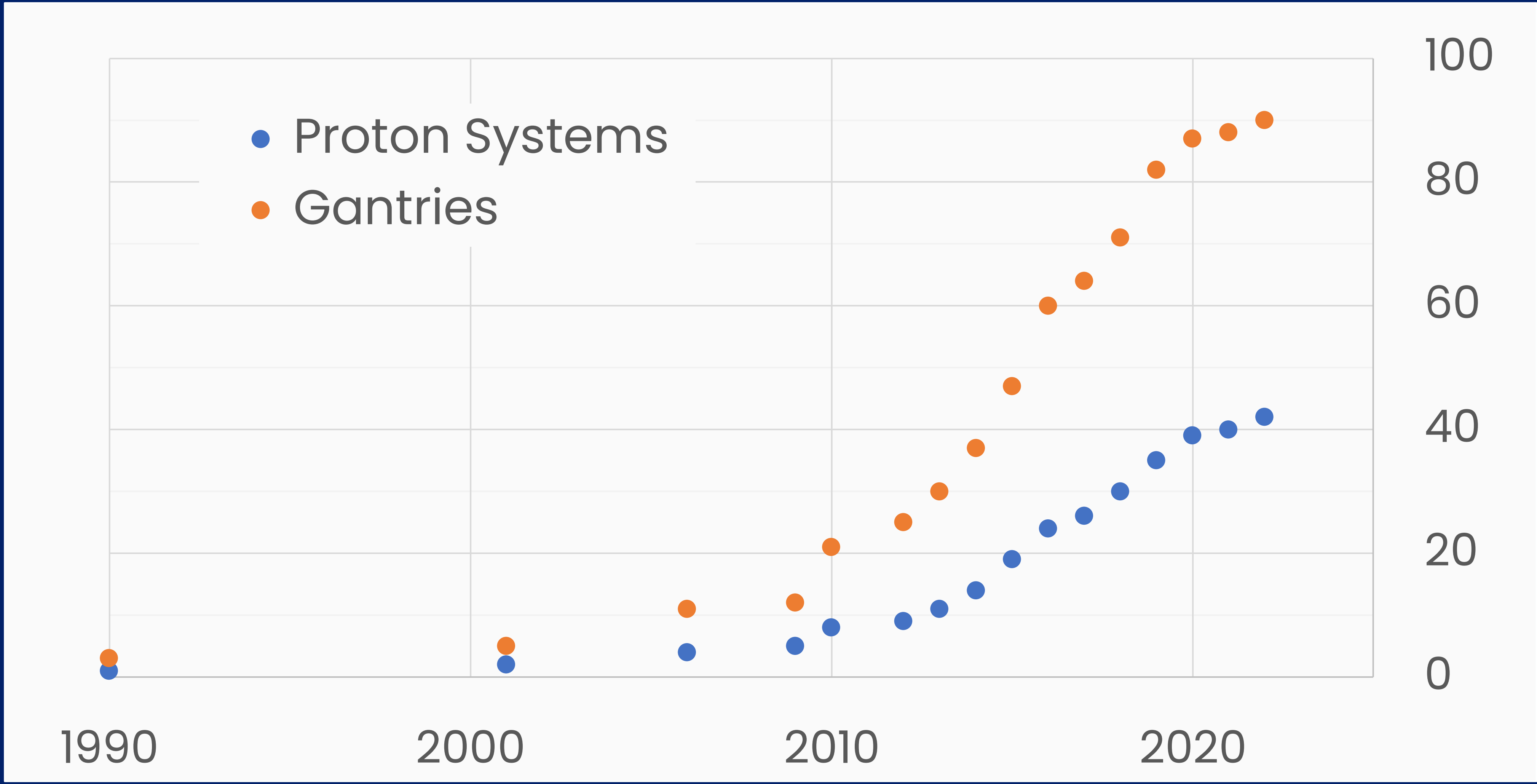
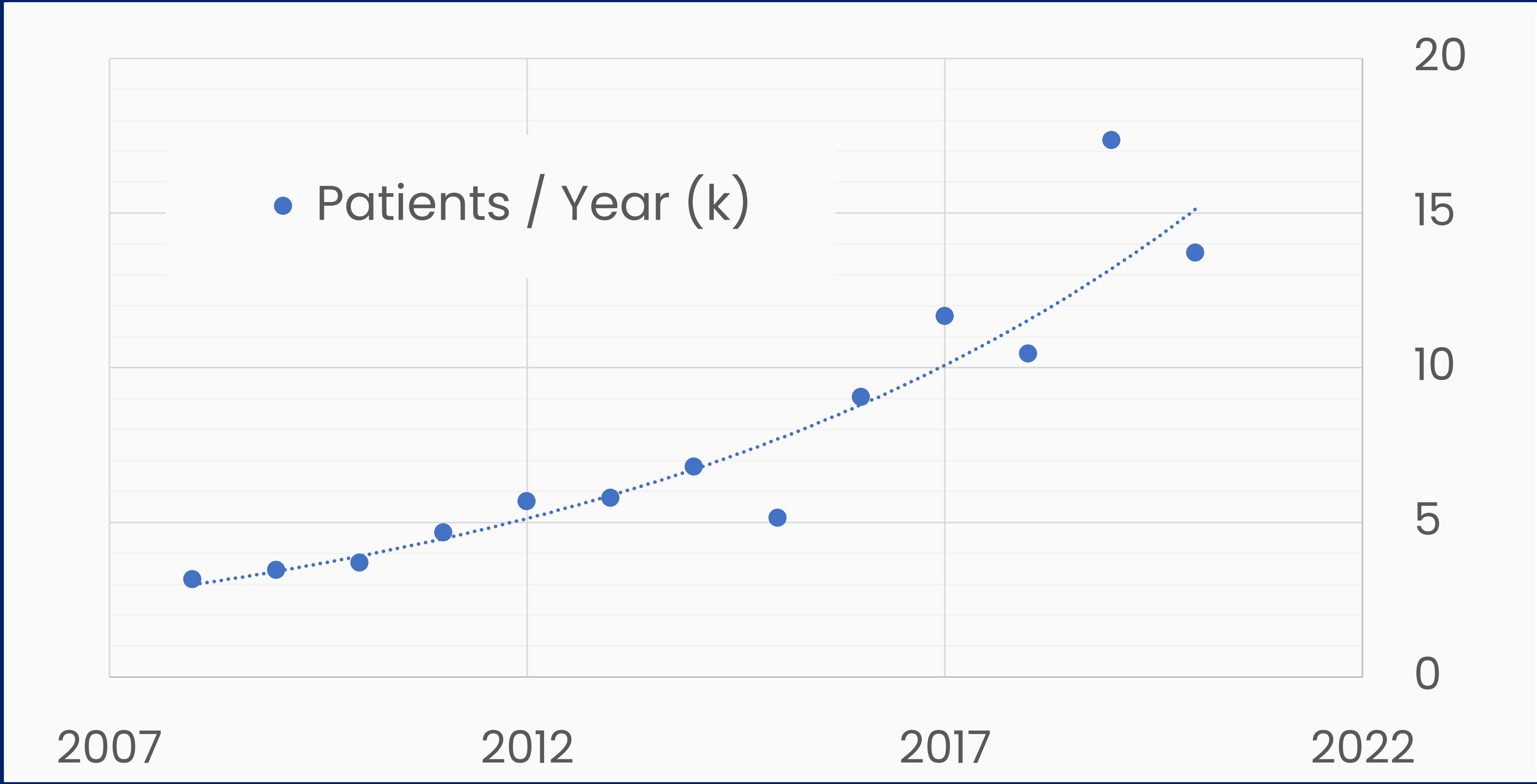
Proton Therapy in the US

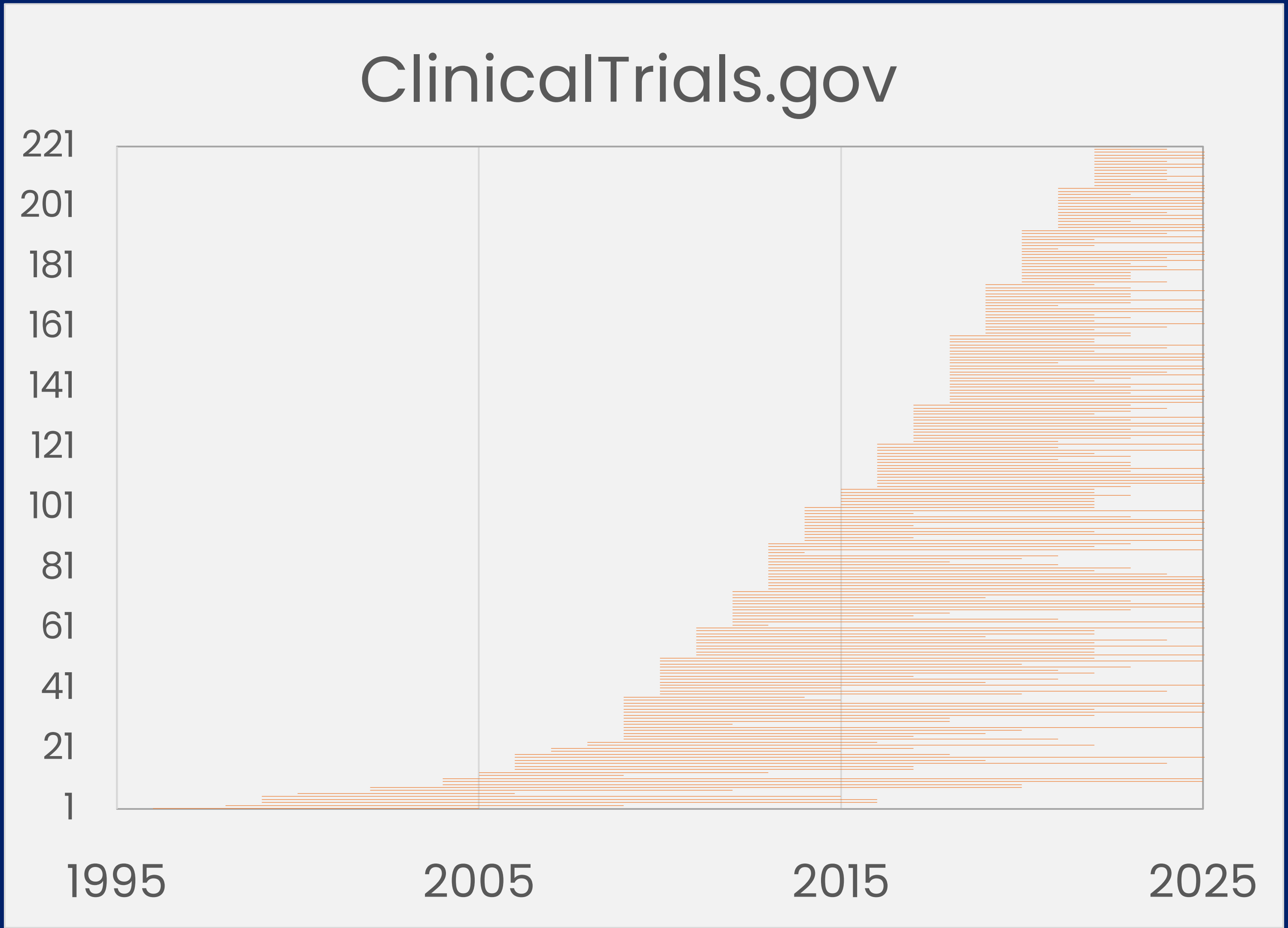


Sources: PTCOG, https://www.ptcog.ch/index.php/facilities-in-operation (2022.07.07)
NAPT, https://www.proton-therapy.org/map/ (2022.07.07)

Proton Therapy in the US



Data extracted from PTCOG, https://www.ptcog.ch/index.php/patient-statistics (2022.07.07)

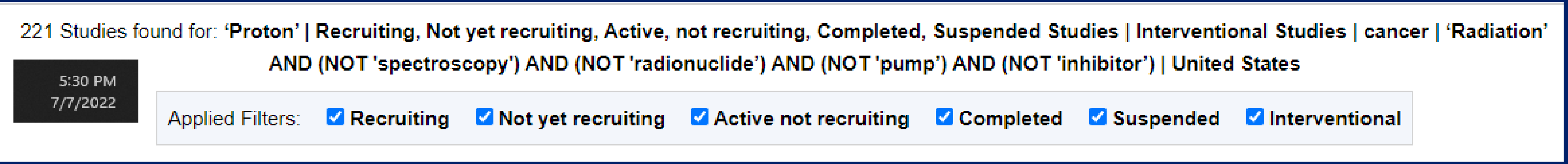


8 in 2002

69 in 2012

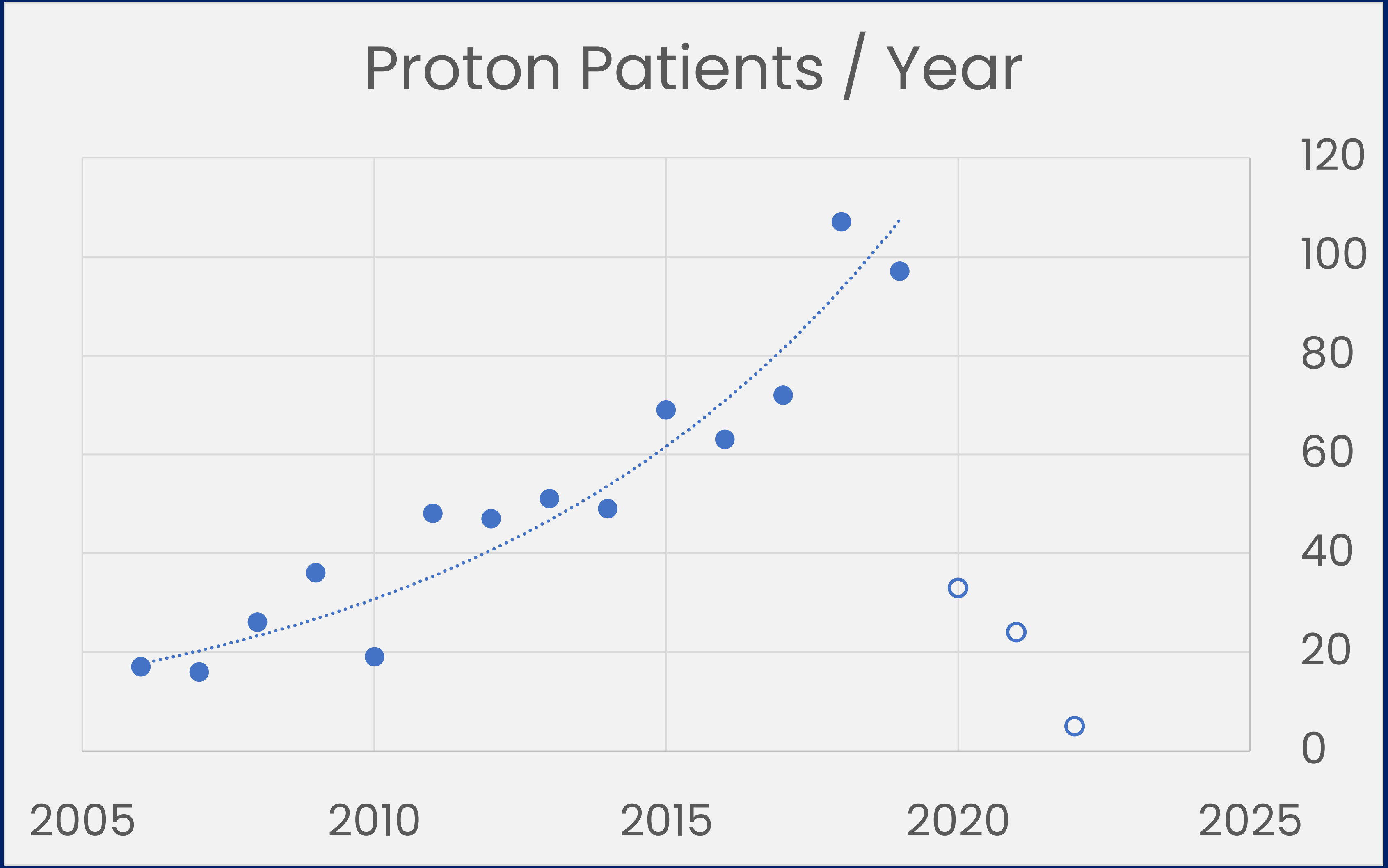
167 in 2022

* Only studies with proton on title or intervention
* Institutional, multi-institutional and cooperative group studies



Cooperative group trials

- COG



Source: Ken Ulin, IROC Rhode Island QA Center

Cooperative group trials

- NRG Oncology
  - 1st Trial allowing protons in 2013 (RTOG-1112)
  - 4 Open trials with proton vs photon
  - 8 Trials allowing protons

Press Releases

May 09 2022

NRG Oncology Study of Photon Versus Proton Therapy for Patients with Newly Diagnosed Glioblastoma Completes Accrual

The NRG-BN001 Study is the First NCI NCTN Proton Therapy Trial to Complete Accrual

The NRG Oncology clinical trial BN001, which is comparing a more dose-intensified radiation therapy schedule to the standard dose of radiation therapy, has recently reached the accrual target. NRG-BN001 is the first National Cancer Institute (NCI)-funded randomized clinical trial of proton therapy within the NCI National Clinical Trials Network (NCTN) to complete accrual. Read more

Source: Ying Xiao, NRG
https://www.nrgoncology.org/Home/News/Newsletters

Other large scale proton trials

- PCORI
  - RADCOMP - Comparing Two Types of Radiation Treatment for Patients with Breast Cancer
    - 2016, randomized controlled trial, 1278 patients
  - COMPPARE - Comparing Radiation Treatments for Localized Prostate Cancer
    - 2018, pragmatic clinical trial, 3000 patients

Source: https://www.pcori.org/, https://comppare.org/, https://www.radcomp.org/

Registries

- PPCR - Pediatric Proton/Photon Consortium Registry
  - Since 2012, 22 Institutions, 3936 Proton patients

- PCG – Proton Collaborative Group
  - Since 2009, 20 Institutions, 23209 patients
  - Clinical trials, 566 patients

Source: T. Yock (PPCR), J. Plochocki-Smallwood (PCG)

ICRU Report 78 (2007)

- Prescribing, Recording, and Reporting Proton-Beam Therapy
  - Standardization of techniques and procedures and harmonization of the clinical descriptions of proton treatments with those of other modalities
  - RBE, dosimetry, deliveries, target volumes, DVH, treatment planning, uncertainties, motion management, QA, and prescribing, recording, and reporting treatment

ICRU Report 78 (2007)

It is therefore proposed that, in proton therapy, the PTV be defined relative to the CTV on the basis of lateral uncertainties alone. An adjustment must then be made within the beam-design algorithm to take into account the differences, if any, between the margins needed to account for uncertainties along the beam direction (*i.e.*, range uncertainties) and those included in the so-defined PTV (*i.e.*, based on lateral uncertainties).

AAPM Proton Reports

- 2019, TG-256: Relative biological effectiveness of proton beams in radiation therapy
- 2019, TG-224: Comprehensive proton therapy machine quality assurance
- 2020, TG-185: Clinical commissioning of intensity modulated proton therapy systems
- 2020, TG-202: Physical uncertainties in the planning and delivery of light ion beam treatments
- 2022, TG-290: Respiratory Motion Management for Particle Therapy

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NCI trial proton guidelines

- ‘Substantial concerns persist as protons are more sensitive than photons to uncertainties in the processes of planning and delivering radiation therapy’
- To ensure safe and consistent proton therapy in multi-institutional cooperative group clinical trials so that neither patient safety nor the study are compromised
- 2007, 2010, 2012, 2019

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NCI proton guidelines - 2019

1. Institution approval by IROC

NCI proton guidelines - 2019

1. Institution approval by IROC

33 US Institutions approved

Passive scattering: 8

Uniform scanning: 6

Pencil beam scanning: 27

Source: http://irochouston.mdanderson.org/RPC/Services/Proton_Approval/Approved_Proton_Centers.htm

IROC proton approval

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- Evaluation of institution's general ability to deliver proton therapy treatments
- Steps
  - Questionnaire
  - Baseline phantom irradiation
  - On-site audit
  - Annual dose monitoring

IROC on-site audits

- Reviews of
  - Dose absolute/relative, IGRT, CT-RPSP
  - QA program
  - Clinical practice
- Recommendations for
  - Best practices
  - Consistency among proton centers

IROC on-site audits

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Deficiencies observed during Imaging and Radiation Oncology Core site visits

Deficiency observed	% of audits resulting in recommendation
TG-40, TG-142, and TG-224 compliance*	97%
CTN-RLSP conversion	59%
QA procedures	53%
Dose calculation/beam modeling	32%
Clinical practice	13%
QA equipment	11%
Image guided radiation therapy	8%
Beam output	5%
Patient QA	5%

Source: Taylor PA, Lowenstein J, Followill D, Kry SF. The Value of On-Site Proton Audits. *Int J Radiat Oncol Biol Phys*. 2022;112(4):1004-1011

Table 1 Irradiations for each phantom type and delivery modality with associated phantom passing criteria and pass rates

Phantom type	Head	Liver	Lung	Prostate	Spine
TLD criteria	5%	7%	7%	7%	7%
Gamma criteria	5%/3 mm	7%/4 mm	7%/5 mm	7%/4 mm	N/A
Gamma threshold	85%	85%	85%*	85%	N/A
Overall pass rate	100%	38%	79%	76%	81%

Source: Taylor PA, Kry SF, Alvarez P, et al. Results From the IROC Houston's Anthropomorphic Phantoms Used for Proton Therapy Clinical Trial Credentialing. *Int J Radiat Oncol Biol Phys*. 2016;95(1):242-248

NCI trial proton guidelines

- 2007, 2010, 2012, 2019

  1. Institution approval by IROC
  2. Institution credentialling for protocol

Institution credentialling for protocol

- Evaluation of institution's ability to deliver proton therapy treatment according to specific protocol
- Procedures
    - Site-Specific phantom irradiation
    - Evidence of experience according to protocol
    - Protocol-specific knowledge assessment
    - Protocol-specific benchmark case
    - IGRT process verification
    - Plan rapid review

NCI proton guidelines

- 2007, 2010, 2012, 2019
  1. Institution approval by IROC
  2. Institution credentialling for protocol
  3. RBE = 1.1, with long term goal of 'robust biological dose'

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4. Monte Carlo dose calculation for heterogeneous sites

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  4. Monte Carlo dose calculation for heterogeneous sites
  5. PTV still there, but error-scenario-based evaluation

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Robustness evaluation

- Robustness is the degree of resilience of desired dose distribution to uncertainties

Source: Yock AD, Mohan R, Flampouri S, et al. Robustness Analysis for External Beam Radiation Therapy Treatment Plans: Describing Uncertainty Scenarios and Reporting Their Dosimetric Consequences. *Pract Radiat Oncol*. 2019;9(4):200-207

Robustness evaluation

- Robustness analysis describes the dosimetric effects of uncertainties by determining dose under instances of uncertainty conditions

Source: Yock AD, Mohan R, Flampouri S, et al. Robustness Analysis for External Beam Radiation Therapy Treatment Plans: Describing Uncertainty Scenarios and Reporting Their Dosimetric Consequences. *Pract Radiat Oncol*. 2019;9(4):200-207

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Robustness analysis is essential for **IMPT**

Source: Yock AD, Mohan R, Flampouri S, et al. Robustness Analysis for External Beam Radiation Therapy Treatment Plans: Describing Uncertainty Scenarios and Reporting Their Dosimetric Consequences. *Pract Radiat Oncol*. 2019;9(4):200-207

Robustness evaluation

- Robustness analysis describes the dosimetric effects of uncertainties by determining dose under instances of uncertainty conditions
    - Full description of uncertainty scenarios

Source: Yock AD, et al. *Pract Radiat Oncol*. 2019;9(4):200-207

Robustness evaluation

- Robustness analysis describes the dosimetric effects of uncertainties by determining dose under instances of uncertainty conditions
    - Full description of uncertainty scenarios
        - Sources, magnitude, likelihood and correlation between sources

Source: Yock AD, et al. *Pract Radiat Oncol*. 2019;9(4):200-207

Scenarios – clinical practice

Q50. Describe common robustness evaluation scenarios for brain

# Scenarios	#	%	±δx /δy/δz (mm)	#	%	±δR (%)	#	%
8	7	35%	3	17	71%	3.5	15	63%
12	6	30%	2	6	25%	3	6	25%
10	2	10%	2.8	1	4%	2	2	8%
9	1	5%				4	1	4%
14	1	5%						
16	1	5%						
21	1	5%						
27	1	5%						
Responses	20		Responses	24		Responses 24		

Q51. Do you combine errors for evaluation?

Response	#	%
No, ±δx, ±δy, ±δz and ±δR, evaluated independently	13	50%
Yes, all errors combined (eg $\pm\sqrt{(\delta x^2 + \delta y^2 + \delta z^2)} \pm\delta R$)	6	23%
Yes, directional setup errors evaluated independently but combined with range errors (eg ±δx±δR)	5	19%
Yes, setup errors combined but independent range error evaluation	1	4%
Other	1	4%
Responses	26	

Source: COG technical proton practice survey sent to IROC approved centers, Jan 2022

Scenarios – trials

Scenario	Setup error			Range error	Other
	R-L	I-S	P-A		
1	$+\delta x$	0	0	0	
2	$-\delta x$	0	0	0	
3	0	$+\delta y$	0	0	
4	0	$-\delta y$	0	0	
5	0	0	$+\delta z$	0	
6	0	0	$-\delta z$	0	
7	0	0	0	$+U$	
8	0	0	0	$-U$	
9	0	0	0	0	Inhale
10	0	0	0	0	Exhale

Scenarios – trials

Scenario	% Range Error	Setup Error (mm)		
		X	Y	Z
1	5.0 %	0	0	0
2	5.0 %	0	0	0
3	0	5.0	0	0
4	0	-5.0	0	0
5	0	0	5.0	0
6	0	0	-5.0	0
7	0	0	0	5.0
8	0	0	0	-5.0

NRG-LU006
(ClinicalTrials.gov NCT #04158141)

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Robustness evaluation

- Robustness analysis describes the dosimetric effects of uncertainties by determining dose under instances of uncertainty conditions
  - Full description of uncertainty scenarios
  - Description of dosimetric consequences

Source: Yock AD, et al. *Pract Radiat Oncol*. 2019;9(4):200-207

Table 1 Elements required for unambiguous reporting of uncertainty scenarios and their dosimetric effects

Element to report	Example(s)
For reporting uncertainty scenarios	
Type of uncertainty	• Lateral translations • Rotations (pitch around lateral axis) • Hounsfield unit uncertainty
Magnitude of uncertainty value	±1 cm
Relative likelihood of uncertainty value	Represented as a probability distribution
Correlation between uncertainties	Covariance matrix for a multivariate normal distribution
Number of sample scenarios	1000 random samples
Determination of dose for each scenario	• Dose recalculated • Dose resampled from the nominal dose distribution
For reporting dosimetric effects of uncertainty scenarios	
Form of the dosimetric representation	• Three-dimensional dose distribution • DVH • Equivalent uniform dose
Dosimetric representation descriptor	• Mean • Standard deviation • Minimum • Maximum • n^{th} percentile
Determination of the dosimetric descriptor	• Minimum DVH as DVH derived from minimum dose per voxel of 3-dimensional dose distributions under uncertainty scenarios • Minimum DVH as dose-bin-wise minimum value of many DVHs under uncertainty scenarios

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Scenarios – trials

Scenario	% Range Error	Setup Error (mm)		
		X	Y	Z
1	5.0 %	0	0	0
2	5.0 %	0	0	0
3	0	5.0	0	0
4	0	-5.0	0	0
5	0	0	5.0	0
6	0	0	-5.0	0
7	0	0	0	5.0
8	0	0	0	-5.0

For plan robustness evaluation, at least 6 of 8 scenarios should achieve CTV coverage >=95% and all scenarios should achieve CTV coverage >=90%. One to 2 scenarios <90% CTV coverage is an acceptable variation. More than 2 scenarios with <90% CTV coverage is an unacceptable deviation.

NRG-LU006
(ClinicalTrials.gov NCT #04158141)

Robustness evaluation – trials

- Pencil beam scanning vs photons

Modality	Dose distribution	Target	Per Protocol	Variation Acceptable	Deviation Unacceptable
Photon		CTV	$D_{100\%} \geq 99\% \, D^{Prescribed}$		$D_{100\%} < 99\% \, D^{Prescribed}$
Proton	Nominal	CTV	$D_{100\%} \geq 99\% \, D^{Prescribed}$		$D_{100\%} < 99\% \, D^{Prescribed}$
Photon		PTV	$D_{100\%} \geq 95\% \, D^{Prescribed}$	$D_{100\%} \geq 90\% \, D^{Prescribed}$	$D_{100\%} < 90\% \, D^{Prescribed}$
Proton	Scenarios	CTV	$D_{100\%} \geq 95\% \, D^{Prescribed}$	$D_{100\%} \geq 90\% \, D^{Prescribed}$	$D_{100\%} < 90\% \, D^{Prescribed}$
Photon		PTV	$D_{10\%} \leq 110\% \, D^{Prescribed}$	$110\% \, D^{Prescribed} < D_{10\%} \leq 120\% \, D^{Prescribed}$	$D_{10\%} > 120\% \, D^{Prescribed}$
Proton	Scenarios	CTV	$D_{10\%} \leq 110\% \, D^{Prescribed}$	$110\% \, D^{Prescribed} < D_{10\%} \leq 120\% \, D^{Prescribed}$	$D_{10\%} > 120\% \, D^{Prescribed}$

Robustness evaluation – trials

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Proton	Scenarios	CTV	$D_{10\%} \leq 110\% D^{Prescribed}$	$110\% D^{Prescribed} < D_{10\%} \leq 120\% D^{Prescribed}$	$D_{10\%} > 120\% D^{Prescribed}$

Robustness evaluation

- Robustness analysis describes the dosimetric effects of uncertainties by determining dose under instances of uncertainty conditions
  - Full description of uncertainty scenarios
  - Description of dosimetric consequences
  - Data representation for robustness analysis

Source: Yock AD, et al. *Pract Radiat Oncol*. 2019;9(4):200-207

NCI proton guidelines

- 2007, 2010, 2012, 2019
  1. Institution approval by IROC
  2. Institution credentialling for protocol
  3. RBE = 1.1, with long term goal of ‘robust biological dose’
  4. Monte Carlo dose calculation for heterogeneous sites
  5. PTV still there, but error-scenario-based evaluation
  6. Proton radiation oncologist and proton medical physicist per protocol

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Role of proton medical physicist

- To define technical requirements, guidelines, and recommendations for safe, consistently high-quality treatments
  - Meticulous QA program to produce optimal dose distributions
  - Training for less experience centers

Protocol physics contribution

1. Proton approval and credentialling requirements

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org		
	Treatment Modality		
	Photon	Proton	Key Information
Facility Questionnaire	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	To determine if your institution has completed the requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	X	X	The appropriate thorax phantom study (3DCRT, IMRT, or proton) provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site (http://irochouston.mdanderson.org). Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually.
Baseline Approval		X	Proton centers must complete baseline approval for participation in the protocol. Details about the proton approval process can be found at http://irochouston.mdanderson.org.
Credentialing Notification Issued to:			
Institution			Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and ECOG-ACRIN that all desired credentialing requirements have been met.

Protocol physics contribution

1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques

Proton beam therapy may be delivered using 3DCPT or IMPT. However, for centers with both techniques available, **use of scanning beams is preferred** due to greater dose conformality to the target and lower dose to organs at risk.

For proton therapy, pencil beam scanning is mandatory. Single scattered, double scattered, and uniform scanning proton therapy is not allowed.

Protocol physics contribution

1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques
3. Motion management
   - Protocol updates according to TG290

Protocol physics contribution

1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques
3. Motion management
4. Planning guidelines
   - Nominal CT, SFO / MFO optimization, 3D/4D optimization, field number/orientation, dose calculation algorithm

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Protocol physics contribution

1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques
3. Motion management
4. Planning guidelines
5. Robustness evaluation

Protocol physics contribution

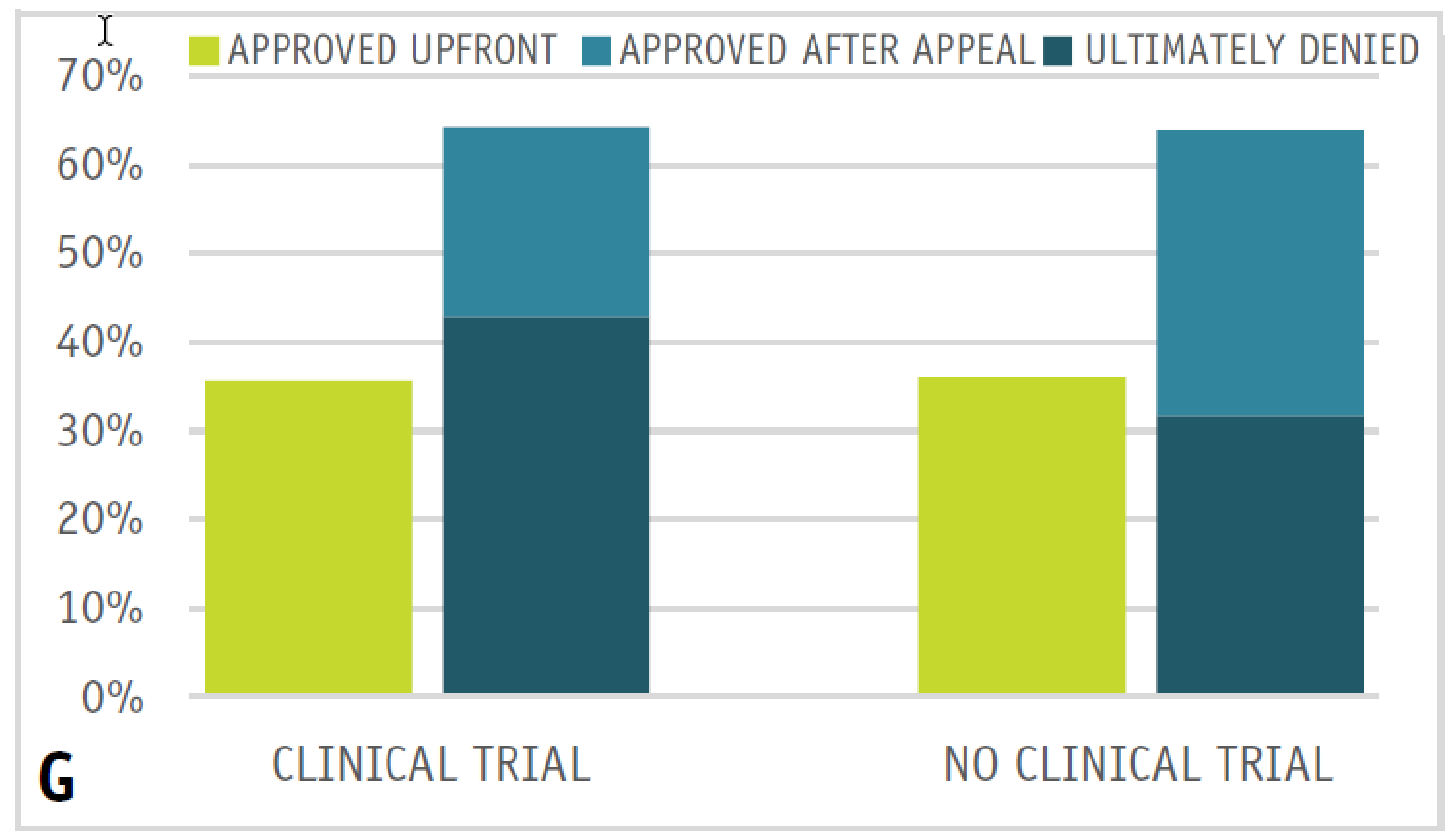
1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques
3. Motion management
4. Planning guidelines
5. Robustness evaluation
6. Dose verification and plan adaptation
   - QACT based evaluation of dose, criteria for re-planning, dose accumulation

Protocol physics contribution

1. Proton approval and credentialling requirements
2. Allowed equipment, modalities, and techniques
3. Motion management
4. Planning guidelines
5. Robustness evaluation
6. Dose verification and plan adaptation
7. Data submission

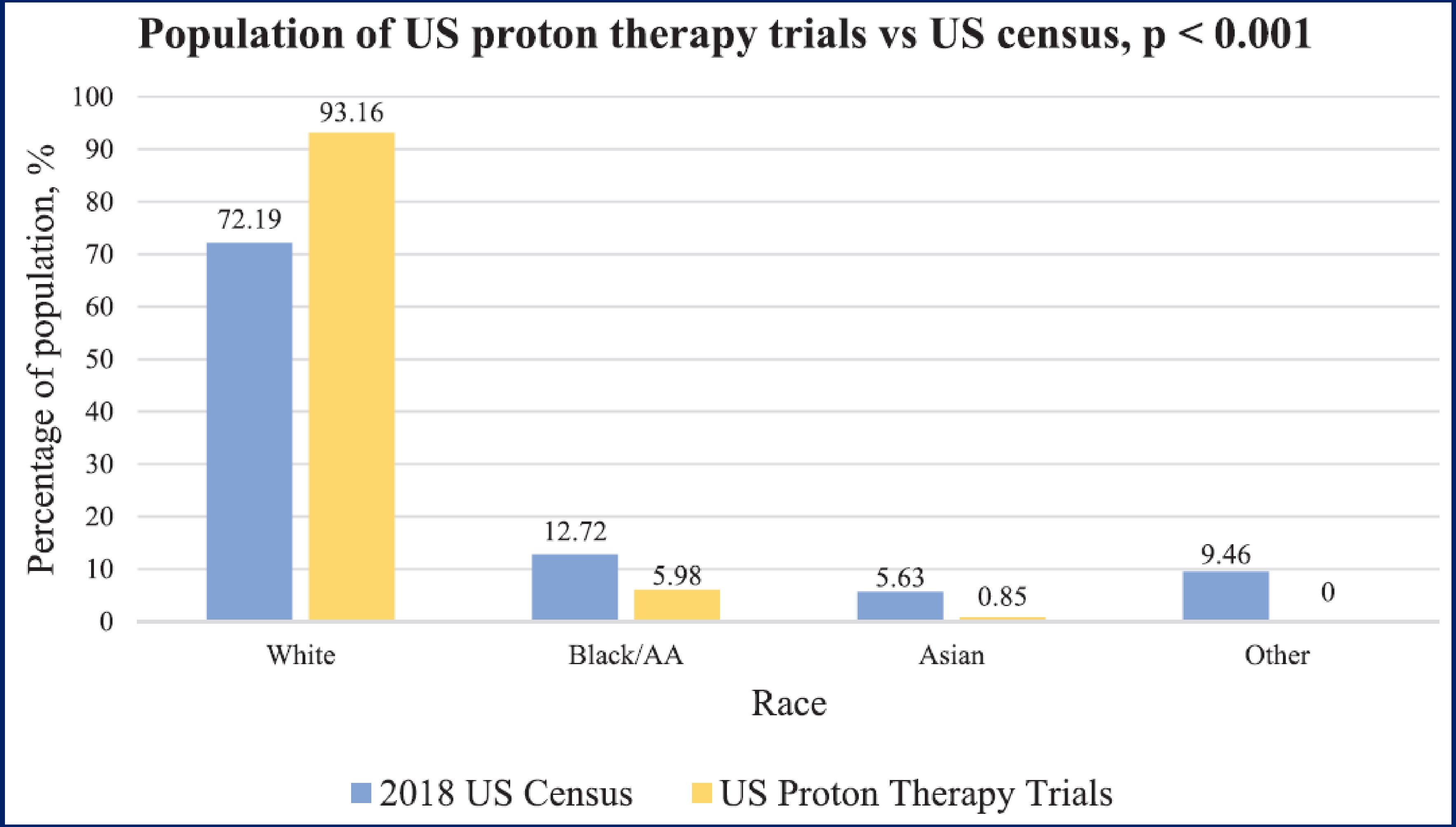
Patients in proton trials

- Insurance coverage matters



Source: Gupta A, Khan AJ, Goyal S, Millevoi R, Elsebai N, Jabbour SK, Yue NJ, Haffty BG, Parikh RR. Insurance Approval for Proton Beam Therapy and its Impact on Delays in Treatment. *Int J Radiat Oncol Biol Phys*. 2019 Jul 15;104(4):714-723

Patient equity in proton trials



Source: Bero EH, Rein LE, Banerjee A, et al. Characterization of Underrepresented Populations in Modern Era Clinical Trials Involving Radiation Therapy. *Pract Radiat Oncol.* 2021; 11(6):453-459

Thank you

and

all the people who responded happily to my requests and questions

For comments, questions or more information: stella.flampouri@emory.edu