

## **Congresso Regionale SIC e SIPAD**

# **INTELLIGENZA ARTIFICIALE, TELEMEDICINA E TECNOLOGIE DIGITALI NELLA CURA DEI PAZIENTI CON TUMORI DELL'APPARATO DIGERENTE**



**9 APRILE**

**AULA MAGNA**

**Università della Calabria (CS)**





# La Ricerca Internazionale sull'Intelligenza Artificiale del Decisions Lab di UNIRC: dalla Diagnostica sul Covid- 19 agli Scenari Applicativi Futuri

- ▶ Prof. Massimiliano Ferrara  
Università "Mediterranea" di Reggio Calabria  
&  
Bocconi ICRIOS



[www.decisionslab@unirc.it](mailto:www.decisionslab@unirc.it)

## *Direttore Scientifico: Massimiliano Ferrara*

*Il Laboratorio di Metodi e Modelli decisionali per le Scienze Sociali promuove l'eccellenza nella ricerca attraverso l'utilizzo di metodi quantitativi per l'analisi delle decisioni individuali e collettive nei fenomeni economici e sociali, con focus in strategie decisionali, data intelligence, project management, economia e management dell'innovazione e della conoscenza.*

# TEAMS



MASSIMILIANO FERRARA

DIRETTORE SCIENTIFICO



BRUNO ANTONIO PANSERA



LUCA GUERRINI



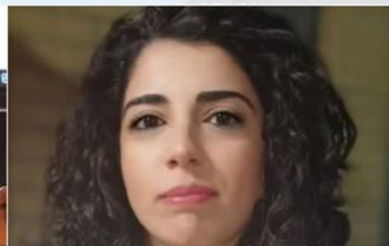
MAURO ALVISI



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# LE NOSTRE COLLABORAZIONI INTERNAZIONALI



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# LE NOSTRE ATTIVITÀ



Promuovere e sostenere la ricerca sia teorica che applicata



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Valorizzare le eccellenze nella ricerca e nel territorio



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Organizzare seminari, convegni, corsi, workshop, lavori di gruppo e scuole di formazione



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Favorire l'innovazione nella didattica con contenuti, metodologie e approcci sperimentali



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Teoria delle Decisioni strategiche



Teoria dei Giochi



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Neuroeconomics



Sistemi di Supporto alle Decisioni



Big Data e Big Data Analytics



Reportistica, OLAP, Data Mining, Machine Learning



Social Network Analysis



Economia e management dell'innovazione e della conoscenza



Program, Project e Risk Management



Geopolitica ed Intelligence economica



NEWS / PROGETTI / RICERCA

## Prime pubblicazioni scientifiche del Gruppo di Ricerca del Prof. Massimiliano Ferrara – Progetto “Dynamics of COVID-19”

A cinque mesi dall’inizio del Progetto sostenuto dall’Università Bocconi – ICRIOS e promosso dal Decisions\_Lab, i primi risultati scientifici ottenuti dal Gruppo di Ricerca coordinato dal Prof. Ferrara, già trovano ...



DECISIONS\_LAB  
FOR COVID-19

NEWS / RICERCA

## Progetto di Ricerca internazionale sulla prevenzione alla diffusione del Covid-19

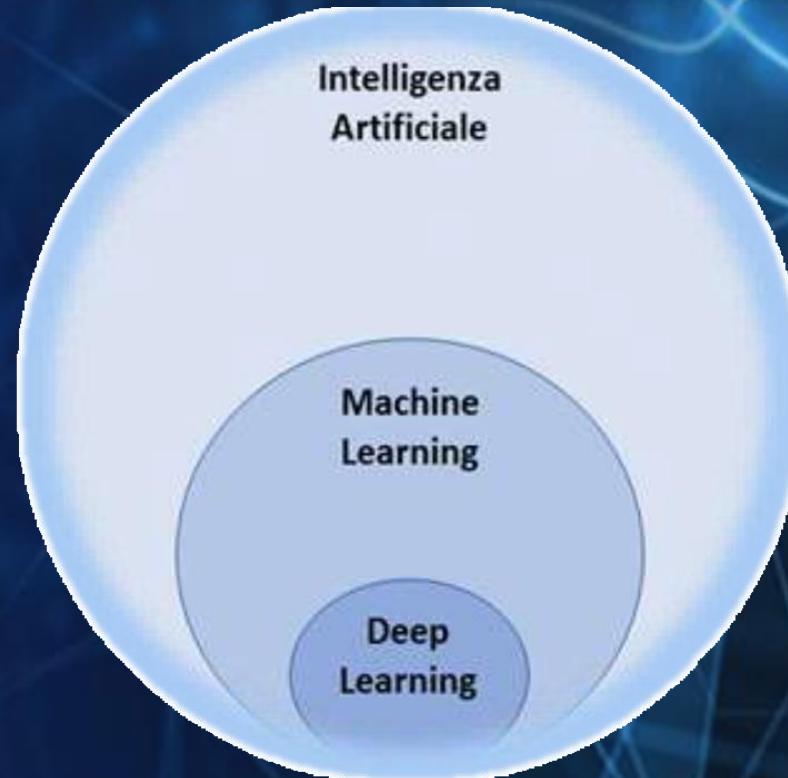
Il Prof. Massimiliano Ferrara, Direttore del Dipartimento di Giurisprudenza, Economia e Scienze Umane (Di.Gi.ES), Research Affiliate presso l’Università Bocconi e Delegato per l’Italia presso l’European Mathematical Society, guiderà un team ...



**L'Intelligenza Artificiale (IA)** (acronimo inglese Artificial Intelligence (AI)) può essere definita come la scienza che si propone di sviluppare macchine intelligenti.



Il **Machine Learning** è un sottoinsieme **dell'Intelligenza Artificiale** e, insieme al **Deep Learning**, costituisce un approccio moderno che sta riscuotendo un notevole successo

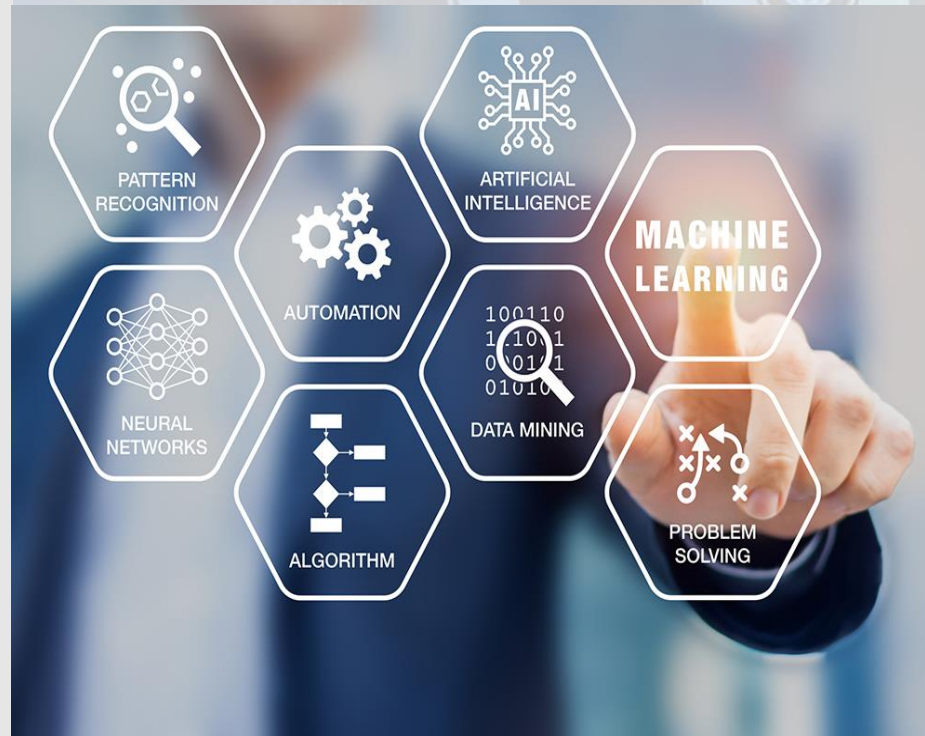


# MACHINE LEARNING E DEEP LEARNING

1

## MACHINE LEARNING

Si occupa principalmente di fare delle previsioni, «imparando» dai dati



2

## DEEP LEARNING

E' un sottoinsieme del Machine Learning ed entra in gioco quando il Machine Learning non riesce ad ottenere i risultati desiderati

# ALGORITMI DI MACHINE LEARNING

## APPRENDIMENTO SUPERVISIONATO



Questi algoritmi utilizzano dataset in cui è già presente la «risposta giusta».

Da questi apprendono ed imparano a prevedere la risposta per un nuovo insieme di dati, che non è presente nell'insieme utilizzato per l'addestramento.

Questi algoritmi utilizzano dataset che non hanno delle risposte disponibili.

E' l'algoritmo stesso che, analizzando i dati, produce delle relazioni tra gli stessi e genera quelle che possono essere le possibili risposte, aiutando a scoprire nuove informazioni presenti nei dati.



## APPRENDIMENTO NON SUPERVISIONATO

# ALGORITMI DI MACHINE LEARNING

## APPRENDIMENTO SEMI SUPERVISIONATO



Questi algoritmi utilizzano dataset in cui la risposta è disponibile solo per una piccola parte degli esempi.

Si proverà, quindi, a sfruttare al meglio i pochi dati con risposta disponibile per ottenere una regola generale da sfruttare per i dati senza risposta

Questi algoritmi non prevedono un dataset di addestramento, per quest non hanno un'esperienza da utilizzare per imparare.

Pertanto da una situazione iniziale qualsiasi e, attraverso regole di premiazione o penalizzazione, cercano di arrivare al risultato ottimale.



## APPRENDIMENTO PER RINFORZO

# FASI DEL MACHINE LEARNING



# scientific reports

 Check for updates

## OPEN Fuzzy rank-based fusion of CNN models using Gompertz function for screening COVID-19 CT-scans

Rohit Kundu<sup>1</sup>, Hritam Basak<sup>1</sup>, Pawan Kumar Singh<sup>2</sup>, Ali Ahmadian<sup>3,4</sup>,  
Massimiliano Ferrara<sup>4</sup> & Ram Sarkar<sup>5</sup>

DECISIONS\_LAB..  
**FOR COVID-19**  
Il Team di Ricerca  
Le Pubblicazioni



## **Fuzzy rank-based fusion of CNN models using Gompertz function for screening COVID-19 CT-scans**

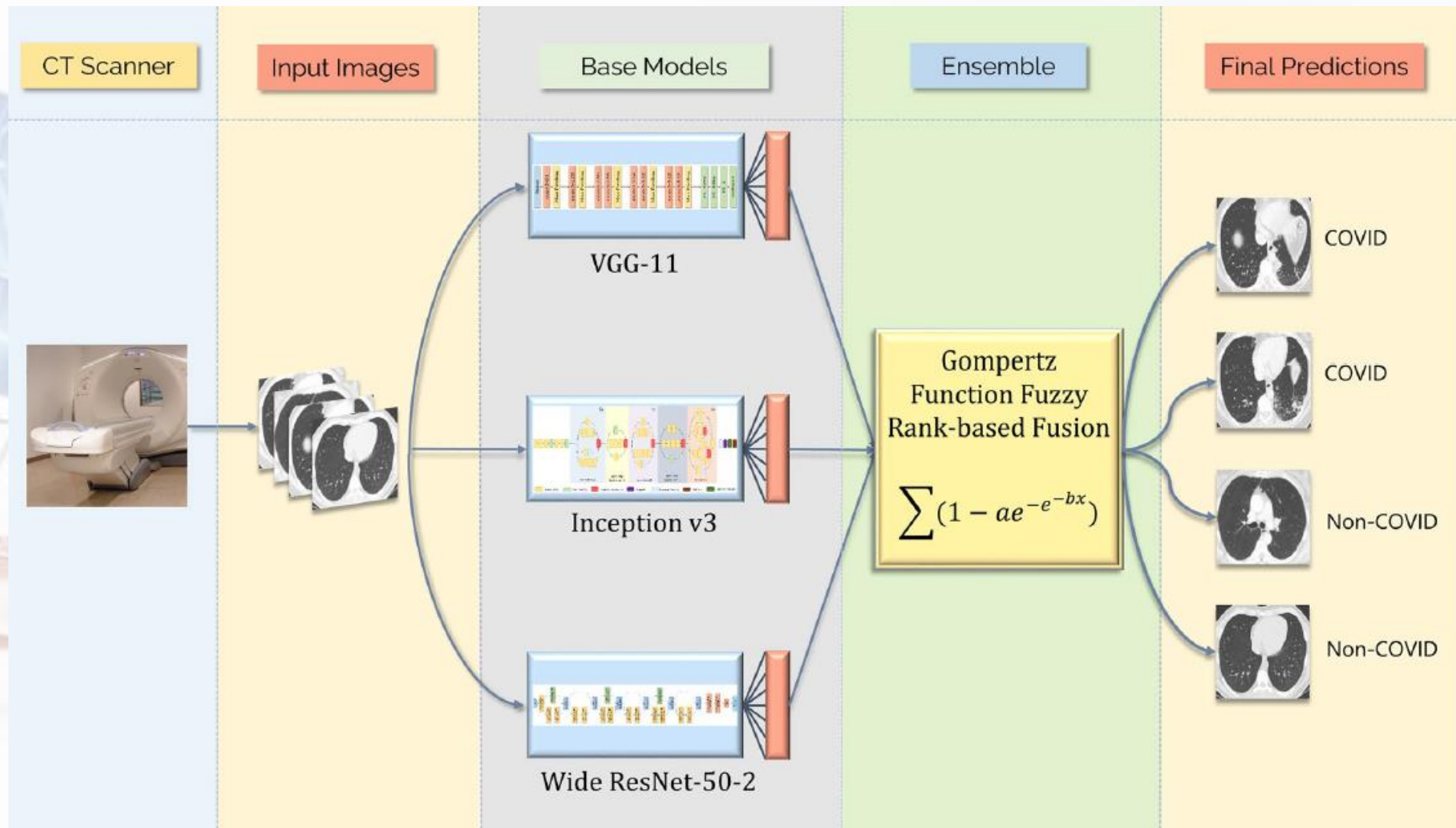
- C'è un disperato bisogno di una diagnosi precoce e accurata di COVID-19 per prevenire ancora di più la diffusione della malattia.
- L'attuale test RT-PCR gold standard è sensibile solo al 71% ed è un test laborioso da eseguire, che porta all'incapacità di condurre lo screening a livello di popolazione.
- A tal fine, in questo articolo, proponiamo un sistema di rilevamento automatizzato del COVID-19 che utilizza immagini TC-scan dei polmoni per classificare gli stessi in casi COVID-19 e non-COVID.





# Fuzzy rank-based fusion of CNN models using Gompertz function for screening COVID-19 CT-scans

- Il metodo proposto applica una strategia d'insieme che genera ranghi fuzzy dei modelli di classificazione di base utilizzando la funzione di Gompertz e fonde i punteggi decisionali dei modelli di base in modo adattivo per fare le previsioni finali sui casi di test.
- Vengono utilizzati tre modelli di rete neurale convoluzionale basati sull'apprendimento del trasferimento, vale a dire VGG-11, Wide ResNet-50-2 e Inception v3, per generare i punteggi decisionali da fondere con il modello d'insieme proposto.
- Il framework è stato valutato su due set di dati di TC del torace pubblicamente disponibili ottenendo prestazioni allo stato dell'arte, giustificando l'affidabilità del modello.
- I codici sorgente rilevanti relativi al presente lavoro sono disponibili in: [GitHub](#).



*Overall workflow of the proposed framework. The CT Scanner image (open access) is obtained from the Progressive Diagnostic Imaging website and the chest CT scan images are from the SARS-COV-2 dataset used in this research.*

		True Class	
		COVID	Non-COVID
Predicted Class	COVID	True Positive 372	False Positive 4
	Non-COVID	False Negative 4	True Negative 365

**(a)** SARS-COV-2 dataset

		True Class	
		COVID	Non-COVID
Predicted Class	COVID	True Positive 644	False Positive 6
	Non-COVID	False Negative 9	True Negative 592

**(b)** Harvard Dataverse dataset

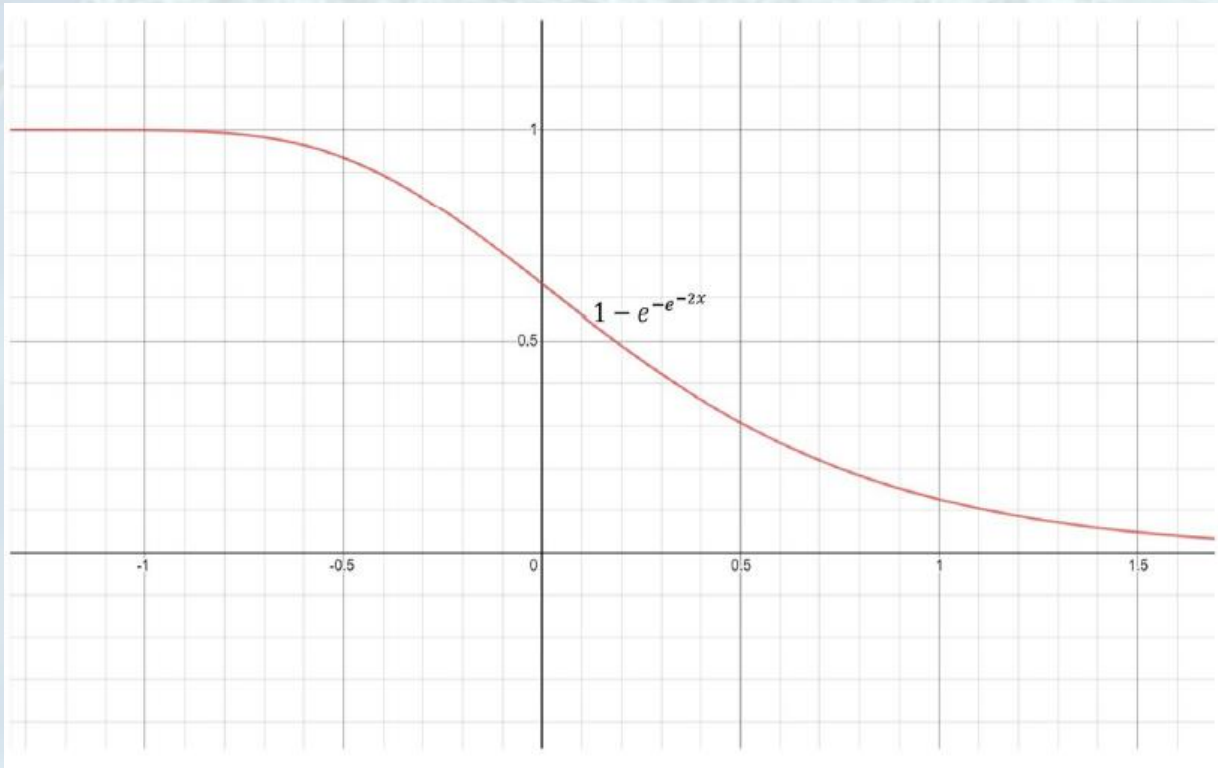
*Confusion matrices obtained by the proposed ensemble model on the two datasets considered in the present work.*

Let there be  $M$  number of decision scores (confidence factors of classifiers)  $\{CF^1, CF^2, \dots, CF^M\}$  for each image  $\mathbf{I}$ . In our case,  $M = 3$ , since we have used three CNN models to generate the confidence scores on the datasets. The decision scores are normalized which follow Eq. (1), where  $C$  is the number of classes in the dataset.

$$\sum_{c=1}^C CF_c^{(i)} = 1.0; \forall i, i = 1, 2, 3, \dots, M \quad (1)$$

Corresponding to all samples belonging to different classes in the dataset, the confidence scores are used to generate the fuzzy ranks. The fuzzy rank for a class  $c$  using the  $i^{th}$  classifier's confidence scores is generated by the Gompertz function as in Eq. (2).

$$R_c^{(i)} = \left(1 - \exp\left[-\exp\left[-2.0 \times CF_c^{(i)}\right]\right]\right), \forall i, c; i = 1, 2, \dots, M; c = 1, 2, \dots, C \quad (2)$$



- The value of  $R_c^{(i)}$  lies in the range [0.127, 0.632] where the smallest value 0.127 is analogous to rank 1 (best rank), i.e., a higher confidence gives a lower (better) value of rank.

- Now, if  $K^i$  represents the top  $k$  ranks, i.e. ranks 1, 2, ...,  $k$ , corresponding to class  $c$ , the fuzzy rank sum (FRSc) and the complement of confidence factor sum (CCFSc) are calculated as in Eqs. (3) and (4), respectively.

*Displaying the re-parameterized Gompertz function used in the present study*

$$FRS_c = \sum_{i=1}^M \begin{cases} R_c^{(i)}, & \text{if } R_c^{(i)} \in K^{(i)} \\ P_c^R, & \text{otherwise} \end{cases} \quad (3)$$

$$CCFS_c = \frac{1}{M} \sum_{i=1}^M \begin{cases} CF_c^{(i)}, & \text{if } R_c^{(i)} \in K^{(i)} \\ P_c^{CF}, & \text{otherwise} \end{cases} \quad (4)$$

$P_c^R$  and  $P_c^{CF}$  are the penalty values imposed on class  $c$ , if it does not belong to the top  $k$  class ranks. The value of  $P_c^R$  is 0.632, which is calculated by putting  $CF_c^{(i)} = 0$  in Eq. (2), and the value of  $P_c^{CF}$  is set to 0.0. The penalty values ensure that class  $c$  does not become an unlikely winner. The final decision score is realized by the product of  $FRS_c$  and  $CCFS_c$  which is used to generate the final predictions of the ensemble model. The final decision score ( $FDS$ ) is calculated as in Eq. (5).

$$FDS_c = FRS_c \times CCFS_c \quad (5)$$

The final predicted class of instance  $\mathbf{I}$  of the dataset is calculated by finding the class having the minimum  $FDS$  value and is given in Eq. (6).

$$class(\mathbf{I}) = \arg \min_{c=1,2,\dots,C} \{FDS_c\} \quad (6)$$

The computational complexity of the proposed ensemble approach is  $O(n)$  where ' $n$ ' is the number of classes in the dataset.



**OPEN** **MRFGRO: a hybrid meta-heuristic feature selection method for screening COVID-19 using deep features**

Arijit Dey<sup>1</sup>, Soham Chattopadhyay<sup>2</sup>, Pawan Kumar Singh<sup>3</sup>, Ali Ahmadian<sup>4,5,7</sup>,  
Massimiliano Ferrara<sup>6</sup>, Norazak Senu<sup>7</sup> & Ram Sarkar<sup>8</sup>



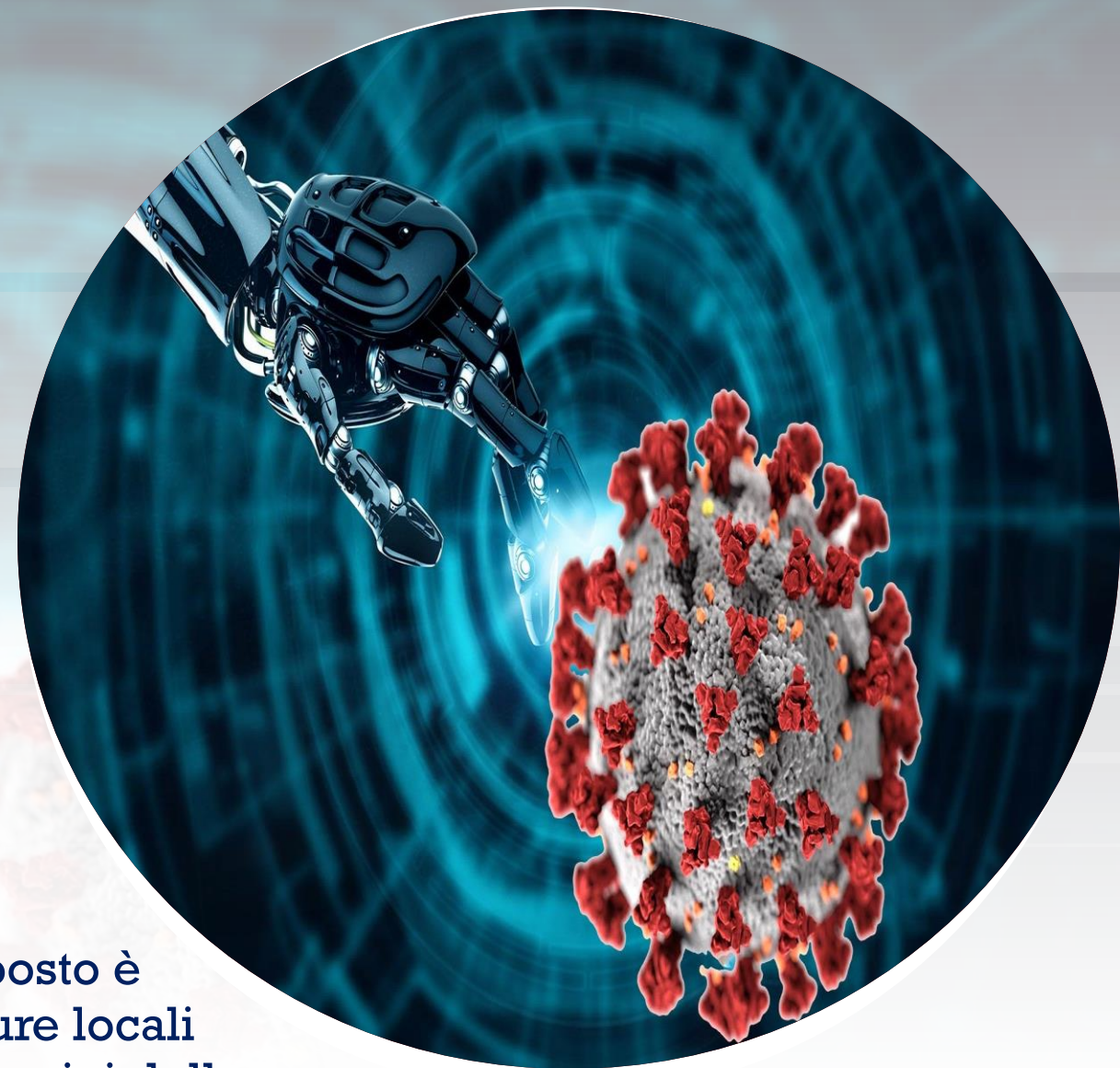
# **MRFRO: a hybrid meta-heuristic feature selection method for screening COVID-19 using deep features**

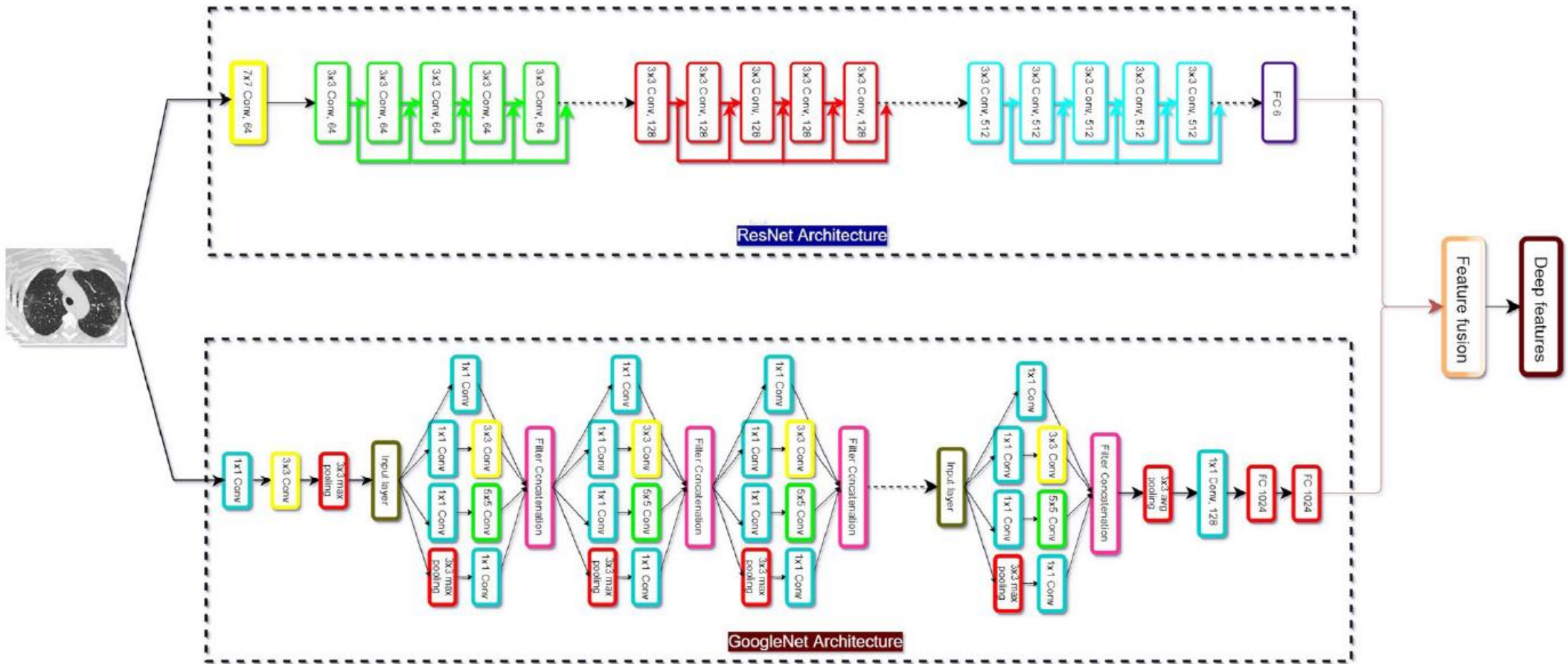
- Il modo più comune per la diagnosi di COVID-19 è la reazione a catena della trascrizione inversa della polimerasi (RT-PCR) in tempo reale che richiede una notevole quantità di tempo per ottenere il risultato.
- L'analisi dell'immagine medica basata su computer è più vantaggiosa per la diagnosi di tale malattia in quanto può fornire risultati migliori in meno tempo.
- Le scansioni di tomografia computerizzata (TC) vengono utilizzate per monitorare le malattie polmonari, incluso il COVID-19.
- In questo lavoro è stato sviluppato un modello ibrido per il rilevamento di COVID-19 che ha due fasi chiave.
- Nella prima fase, abbiamo messo a punto i parametri delle reti neurali convoluzionali pre-addestrate (CNN) per estrarre alcune caratteristiche dai polmoni affetti da COVID-19.





- Come CNN pre-addestrate, abbiamo utilizzato due CNN standard, ovvero GoogleNet e ResNet18.
- Abbiamo proposto un algoritmo ibrido di selezione delle caratteristiche meta-euristiche (FS), denominato Golden Ratio Optimizer (MRFGRO) basato su Manta Ray Foraging per selezionare il sottoinsieme di caratteristiche più significative.
- Il modello proposto è implementato su tre set di dati pubblicamente disponibili, vale a dire, set di dati COVID-CT, set di dati SARS-COV-2 e set di dati MOSMED, e raggiunge una precisione di classificazione all'avanguardia rispettivamente del 99,15%, 99,42% e 95,57%.
- I risultati ottenuti confermano che l'approccio proposto è abbastanza efficiente rispetto ai descrittori di texture locali utilizzati per il rilevamento di COVID-19 dalle immagini della TC del torace





*Illustration of the work flow of deep features extraction from GoogLeNet and ResNet18 architectures.*

*The input CT-scan images are taken from CARS-Cov-2 CT-scan dataset.*

The mathematical expression of chain foraging is as followed:

$$p_j^{(n+1)} = \begin{cases} p_j^n + d(p_{best}^n - p_j^n) + \beta(p_{best}^n - p_j^n) & j = 1 \\ p_j^n + d(p_{j-1}^n - p_j^n) + \beta(p_{best}^n - p_j^n) & j = 2, \dots, N \end{cases} \quad (3)$$

at iteration  $n$ , the position of  $j$ th manta ray is given by  $p_j^n$  and,  $d$ ,  $N$  and  $p_{best}^n$  are a random vector, number of manta rays and the best solution respectively. The weighting coefficient  $\beta$  is given by

$$2 \times d \times \sqrt{|\log(d)|}. \quad (4)$$

Manta rays start forming chain in a combined manner and swim towards the prey following a spiral path, after being cognizant about the exact position of the plankton. In cyclone foraging, in addition to spiral motion, each manta ray is one step ahead towards its prior one, and thus a cyclonic motion is formed. The cyclonic foraging can be expressed in terms of two perpendicular components, which are given as follows:

$$X_j^{n+1} = X_{best} + d(X_{j-1}^n - X_j^n) + e^{a\omega} \cos(2\pi\omega)(X_{best} - X_j^n), \quad (5)$$

$$Y_j^{n+1} = Y_{best} + d(Y_{j-1}^n - Y_j^n) + e^{a\omega} \sin(2\pi\omega)(Y_{best} - Y_j^n), \quad (6)$$

where  $\omega$  is a random number

Now similar to chain foraging, the position and movement of cyclone foraging towards the minimum can be expressed as given below:

$$p_j^{(n+1)} = \begin{cases} p_{best} + d(p_{best}^n - p_j^n) + \gamma(p_{best}^n - p_j^n) & j = 1 \\ p_{best} + d(p_{j-1}^n - p_j^n) + \gamma(p_{best}^n - p_j^n) & j = 2, \dots, N \end{cases} \quad (7)$$

Here, also  $\gamma$  is a weighting factor with the expression

$$\gamma = 2e^{d_1 \left( \frac{I-n+1}{I} \right)} \sin(2\pi d_1), \quad (8)$$

where  $I$  is the maximum iteration and  $d_1$  is a random number



## ET-NET: an ensemble of transfer learning models for prediction of COVID-19 infection through chest CT-scan images

Rohit Kundu<sup>1</sup>  · Pawan Kumar Singh<sup>2</sup>  · Massimiliano Ferrara<sup>3,4</sup>  ·  
Ali Ahmadian<sup>5,6,7</sup>  · Ram Sarkar<sup>8</sup> 



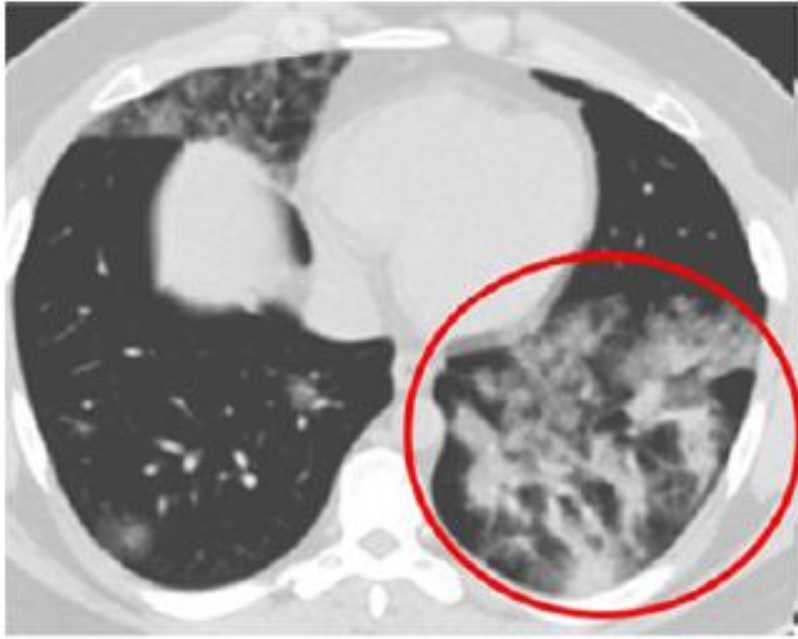
# ET-NET: an ensemble of transfer learning models for prediction of COVID-19 infection through chest CT-scan images

- Sebbene il test in tempo reale della reazione a catena della polimerasi (RT-PCR) sia il test di riferimento per lo screening del COVID-19, non è accurato e sensibile in modo soddisfacente.
- D'altra parte, le immagini della tomografia computerizzata (TC) sono molto più sensibili e possono essere adatte per il rilevamento di COVID-19.
- A tal fine, con questo lavoro si è sviluppato un metodo completamente automatizzato per lo screening rapido di COVID-19 utilizzando immagini di TAC del torace che impiegano tecniche di Deep Learning.

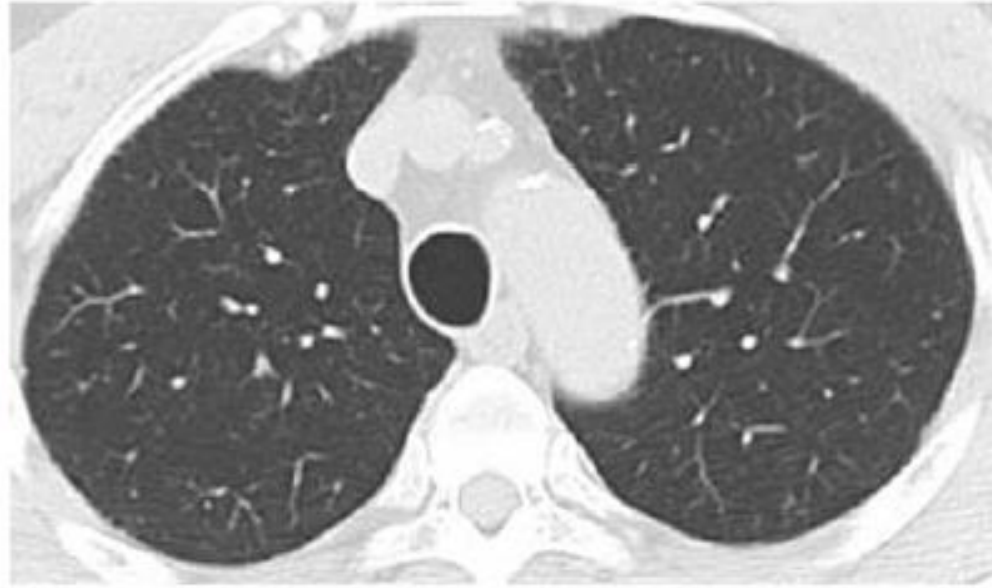


- Per questo problema di classificazione delle immagini supervisionato, è stato utilizzato un insieme di aggregazione bootstrap o Bagging di tre modelli di apprendimento di trasferimento, ovvero Inception v3, ResNet34 e DenseNet201, per aumentare le prestazioni dei singoli modelli.
- Il framework proposto, chiamato ET-NET, è stato valutato su un set di dati pubblicamente disponibile, raggiungendo una precisione del  $97,81 \pm 0,53\%$ , una precisione del  $97,77 \pm 0,58\%$ , una sensibilità del  $97,81 \pm 0,52\%$  e una specificità del  $97,77 \pm 0,57\%$  su un cross-validation di 5 volte. validazione superando dell'1,56% il metodo all'avanguardia sullo stesso set di dati.





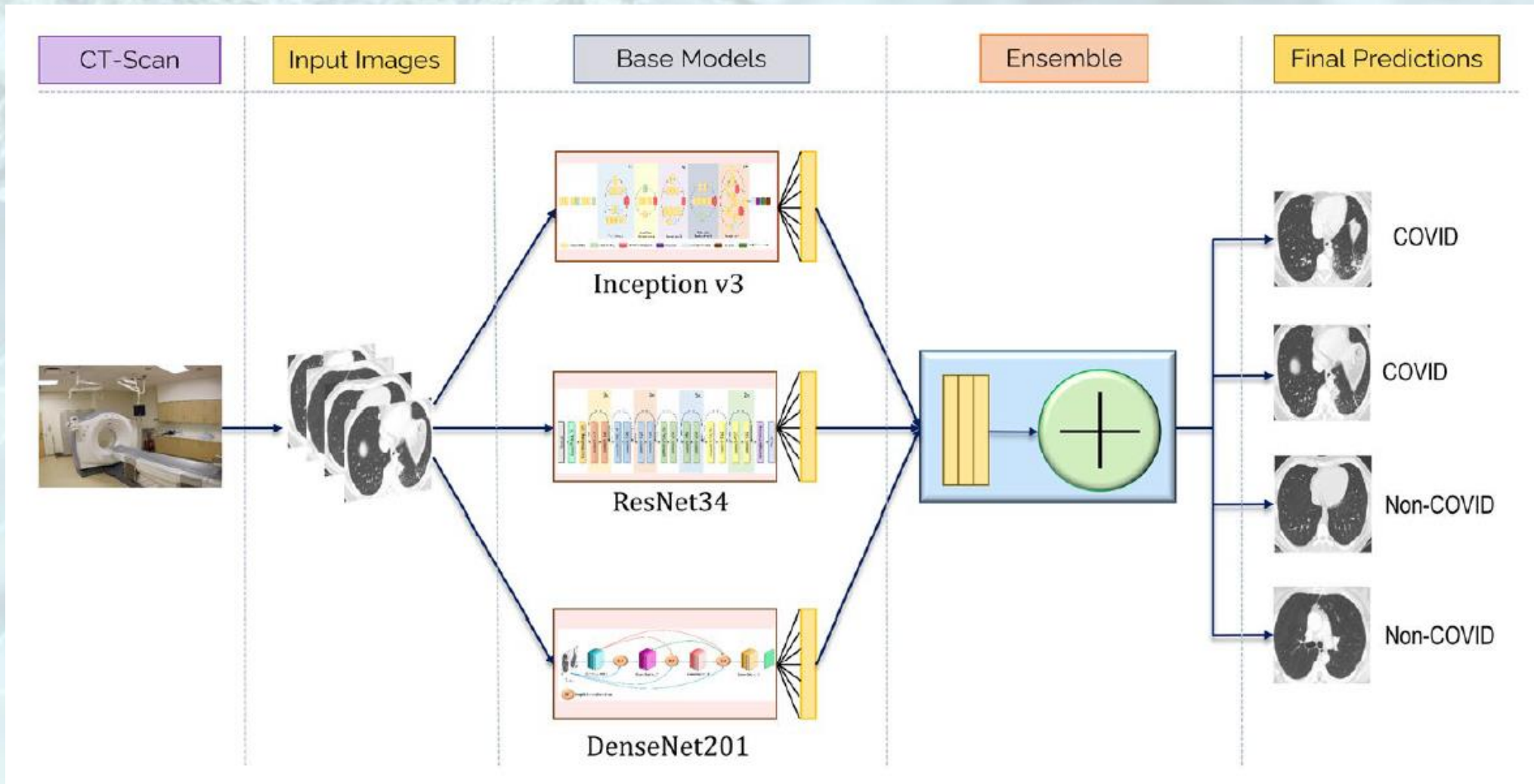
**(a)** COVID-19 positive patient



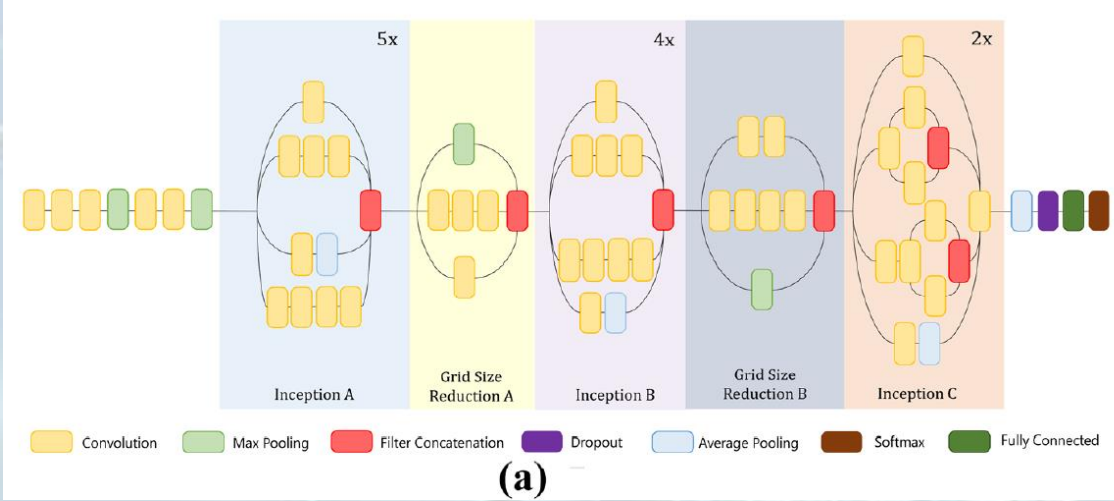
**(b)** COVID-19 negative patient

*Illustration of chest CT image findings of two patients having: (a) COVID-19 positive and (b) COVID-19 negative. The COVID-19 infection's characteristic "Ground Glass Opacity" has been marked with a red circle in the COVID-19 infected chest CT image*

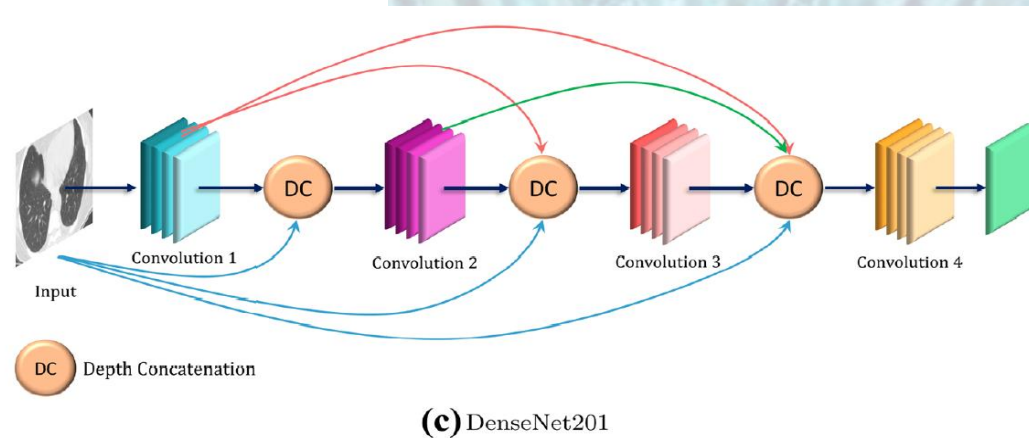
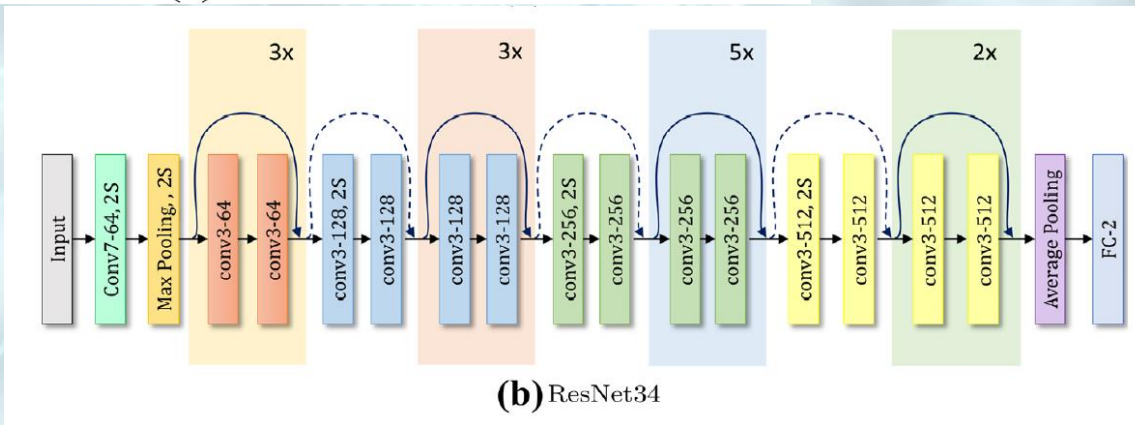




*Overall workflow of the proposed ET-NET ensemble classifier model for COVID-19 detection from chest CT-scan images*



*Architectures of the three CNN base classifiers:  
**(a)** Inception v3, **(b)** ResNet34, and **(c)** DenseNet201 used to form the proposed ensemble model called ET-NET*



**ANALYSIS OF THE MENTAL  
HEALTH OF SCHOOL AND COLLEGE  
STUDENTS DURING THE PANDEMIC:  
ARTIFICIAL INTELLIGENCE  
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*Grazie per l'Attenzione*



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Il sottoscritto Alfonso Recordare

ai sensi dell'art. 76 comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017  
dichiara

di non avere avuto rapporti di natura finanziaria e lavorativa con imprese commerciali  
operanti in ambito sanitario negli ultimi due anni

# INTELLIGENZA “NATURALE” E TRATTAMENTO DELLE INFEZIONI IN CHIRURGIA E NEI PAZIENTI TRAPIANTATI

CON IL PATROCINIO DI



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Università della Calabria

CONGRESSO REGIONALE SIC e SIPAD

**INTELLIGENZA ARTIFICIALE,  
TELEMEDICINA E TECNOLOGIE DIGITALI  
NELLA CURA DEI PAZIENTI CON  
TUMORI DELL'APPARATO DIGERENTE**

*Presidenti: Gianluigi Greco e Bruno Nardo*

# INTELLIGENZA “NATURALE” E TRATTAMENTO DELLE INFEZIONI IN CHIRURGIA E NEI PAZIENTI TRAPIANTATI



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Dipartimento di Chirurgia Oncologica e d'Urgenza,

*Ospedale Dell'Angelo Venezia Mestre*

Professore a contratto Chirurgia Generale

*Tbilisi State Medical University Georgia*



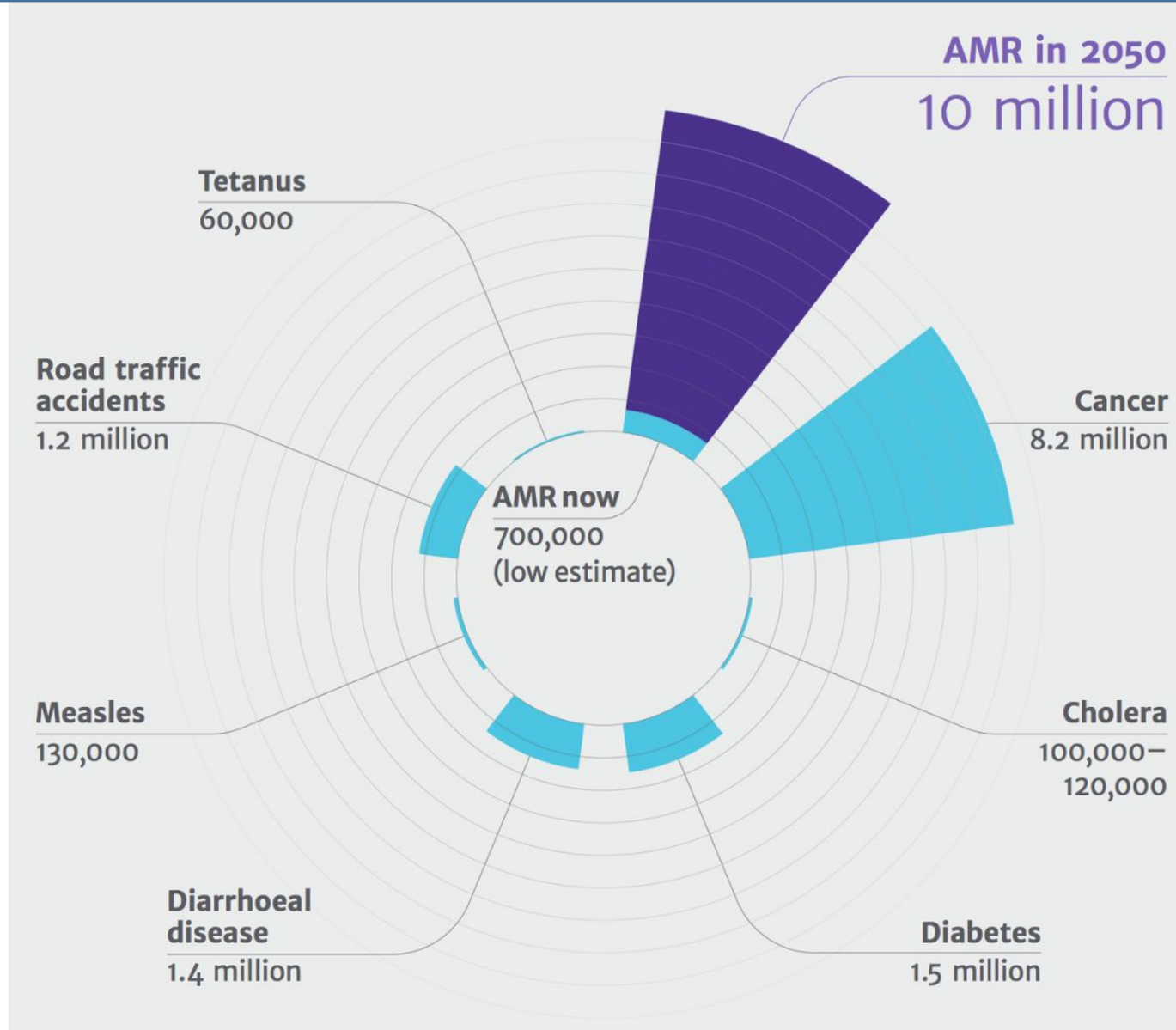
# INTELLIGENZA “NATURALE” E TRATTAMENTO DELLE INFEZIONI IN CHIRURGIA NEI PAZIENTI TRAPIANTATI







# FORECAST

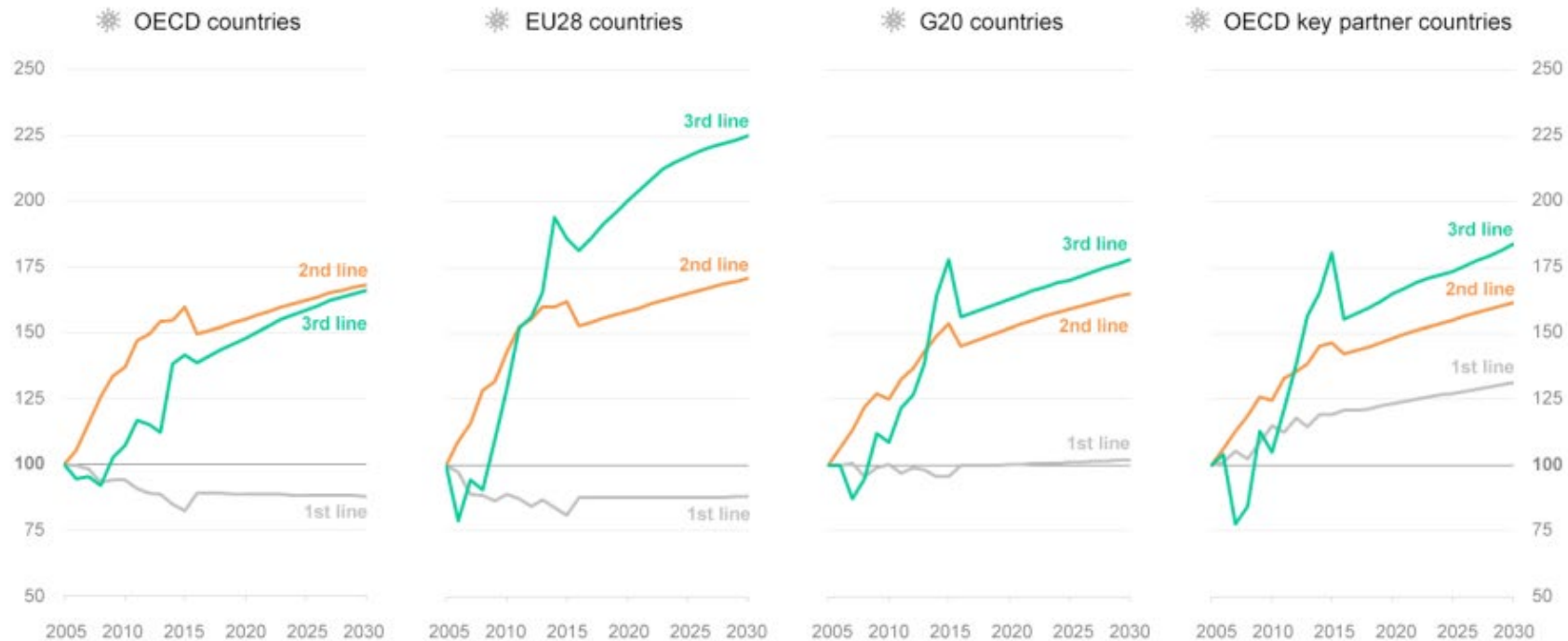


# Trends antimicrobial resistance



## Trends in antimicrobial resistance

Selected regions and country groups among high-priority antibiotic-bacterium combinations, by line of treatment



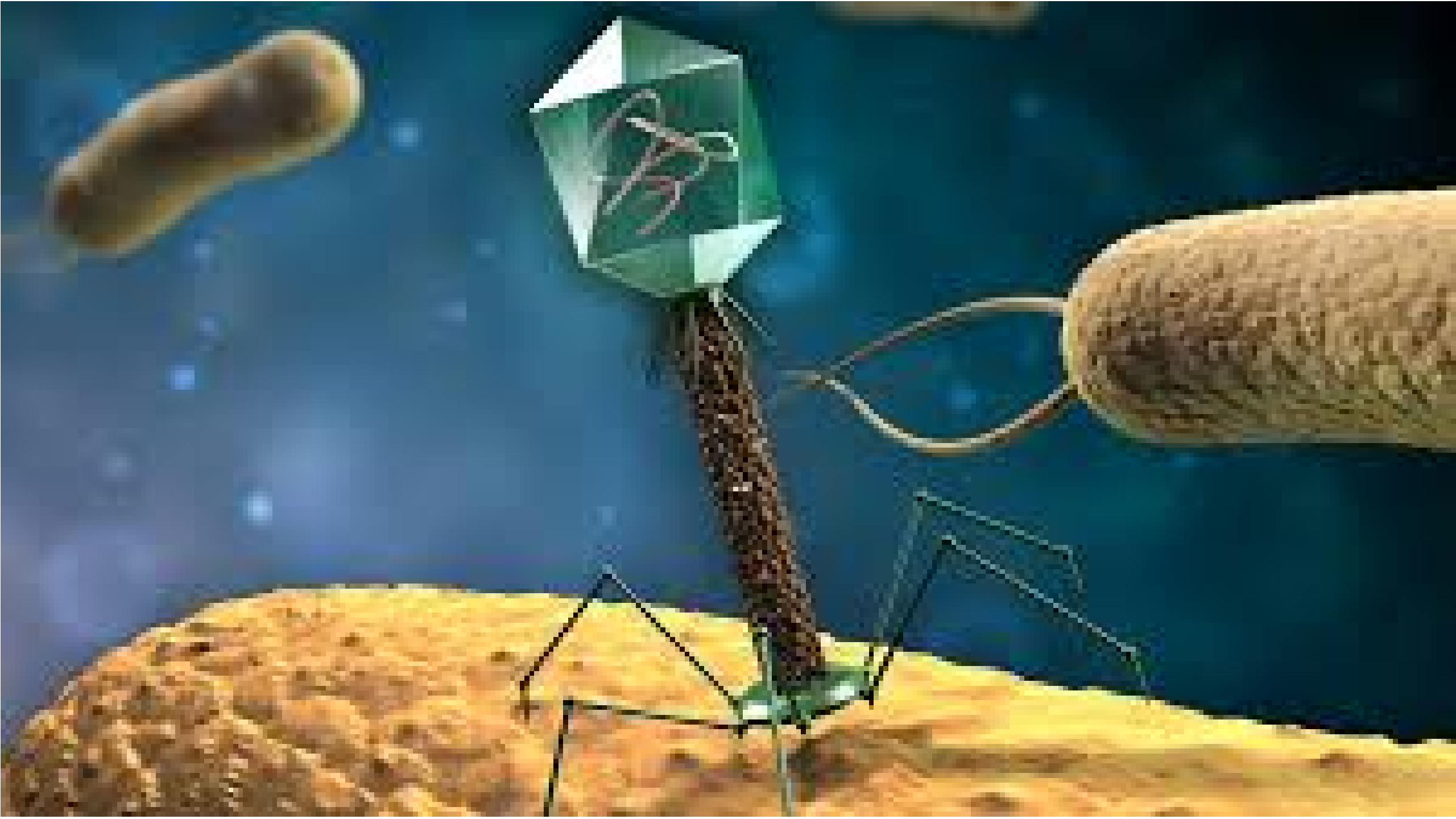
Resistance to **first-line treatments** is defined as the average of the proportions of penicillin-resistant *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus*.

Resistance to **second-line treatments** is the average of the proportions of *E. coli* and *K. pneumoniae* resistant to 3rd-generation cephalosporins and of *E. coli* resistant to fluoroquinolones.

Resistance to **third-line treatments** is defined as the proportion of *K. pneumoniae* resistant to carbapenems.

OECD key partner countries refer to Brazil, China, India, Indonesia and South Africa.

Source: OECD analyses of data from surveillance networks included in ResistanceMap.



# Phage therapy: history

The first evidence for a viral-like agent with antibacterial properties was reported by M. E. Hankin in 1896.

Found in the Ganges river in India, it was temperature sensitive, capable of passing through a porcelain filter, and could reduce titres of the bacterium *Vibrio cholerae* in laboratory culture.

Hankin suggested that it might help to decrease the incidence of cholera in people using water from the Ganges.

Adhya S and C. Merril. 2006. The road to phage therapy. *Nature* **443**: 754-755

# Phage therapy: history

## *d'Herelle's first clinical experiences in 1920's*

d'Herelle F. (1917). Sur un microbe invisible antagoniste des bacilles dysentériques.

Acad. Sci. Ser. D 165:373

d'Herelle F. (1925) Essai de traitement de la peste bubonique par le bactériophage.

La Presse Med. 33: 1393-94.

George Eliava starts the microbiology institute in Tbilisi (1923) and

d'Hérelle is invited by Stalin to the Eliava Institute (1936).

## *Commercialization of phages in France and USA in 1930's*

L'Oréal: Bacté-intesti-phage, Bacté-pyo-phage, Bacté-staphylo-phage

Eli Lilly: Colo-lysate, Entero-lysate, Staphylo-lysate

## *Phage therapy was abandoned in the West, because of*

lack of understanding of the high specificity and mode of action of phages

exaggerated claims of effectiveness: urticaria, herpes, eczema

the rise of **broad-spectrum antibiotics**

*but phage therapy research continued in Eastern Europe ...*

# Eliava Institute – Tbilisi (Georgia)



# Bacteriophages an alternative to the antibiotics



- Long history of success in the former Soviet Union
- Before discovery of antibiotics – it was wide spread in Europe and US (Institut Pasteur, France; Antipiol, Germany; Eli Lilly, US)
- Phage were successfully used for treatment and prophylactic purposes
- For today, Eliava Consortium (Eliava Institute of Bacteriophages, Diagnostic center, production facility, phage therapy center) – the World known center for research and application



# Historical overview

REVIEW

Virulence 5:1, 226–235; January 1, 2014; © 2014 Landes Bioscience

## A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens

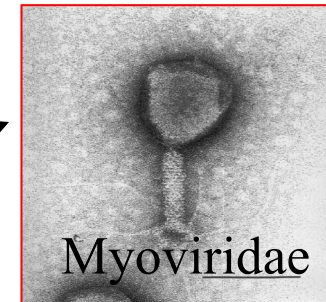
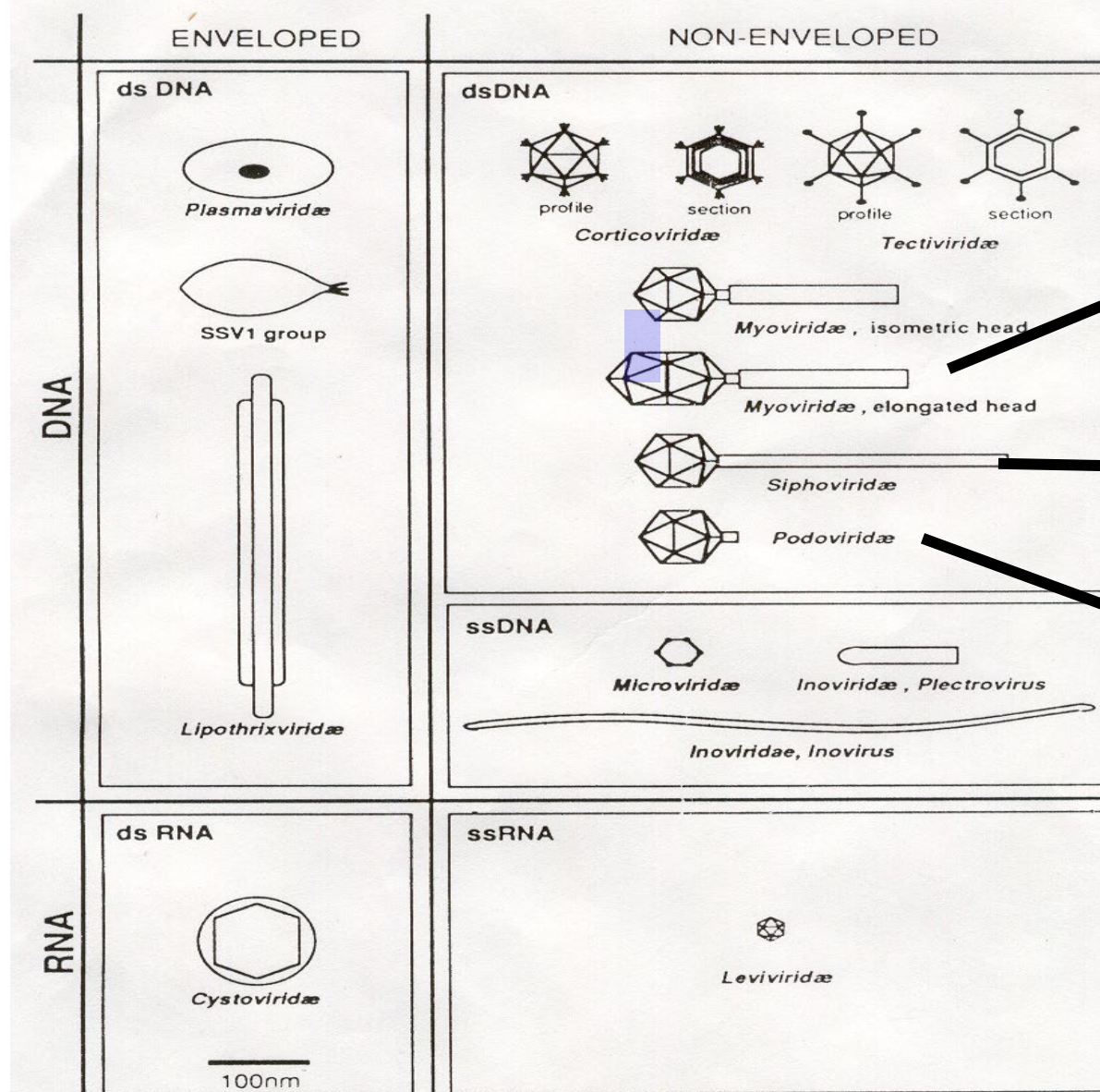
Xavier Wittebole<sup>1,\*</sup>, Sophie De Roock<sup>2</sup>, and Steven M Opal<sup>3,4</sup>

<sup>1</sup>Critical Care Department; St Luc University Hospital; Université Catholique de Louvain; Brussels, Belgium; <sup>2</sup>High Care Burn Unit; Military Hospital; Brussels, Belgium;

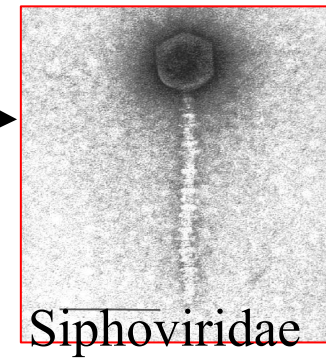
<sup>3</sup>The Infectious Disease Division; Memorial Hospital of RI; Providence, RI USA; <sup>4</sup>The Alpert Medical School of Brown University; Providence, RI USA

**Keywords:** sepsis, septic shock, multidrug resistant pathogens, bacteriophage therapy, phage therapy

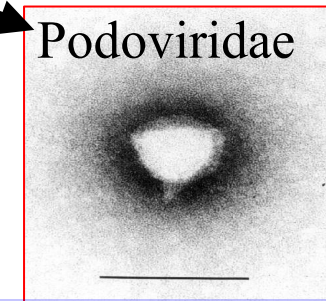
# Phages: genome and virion structure



25%



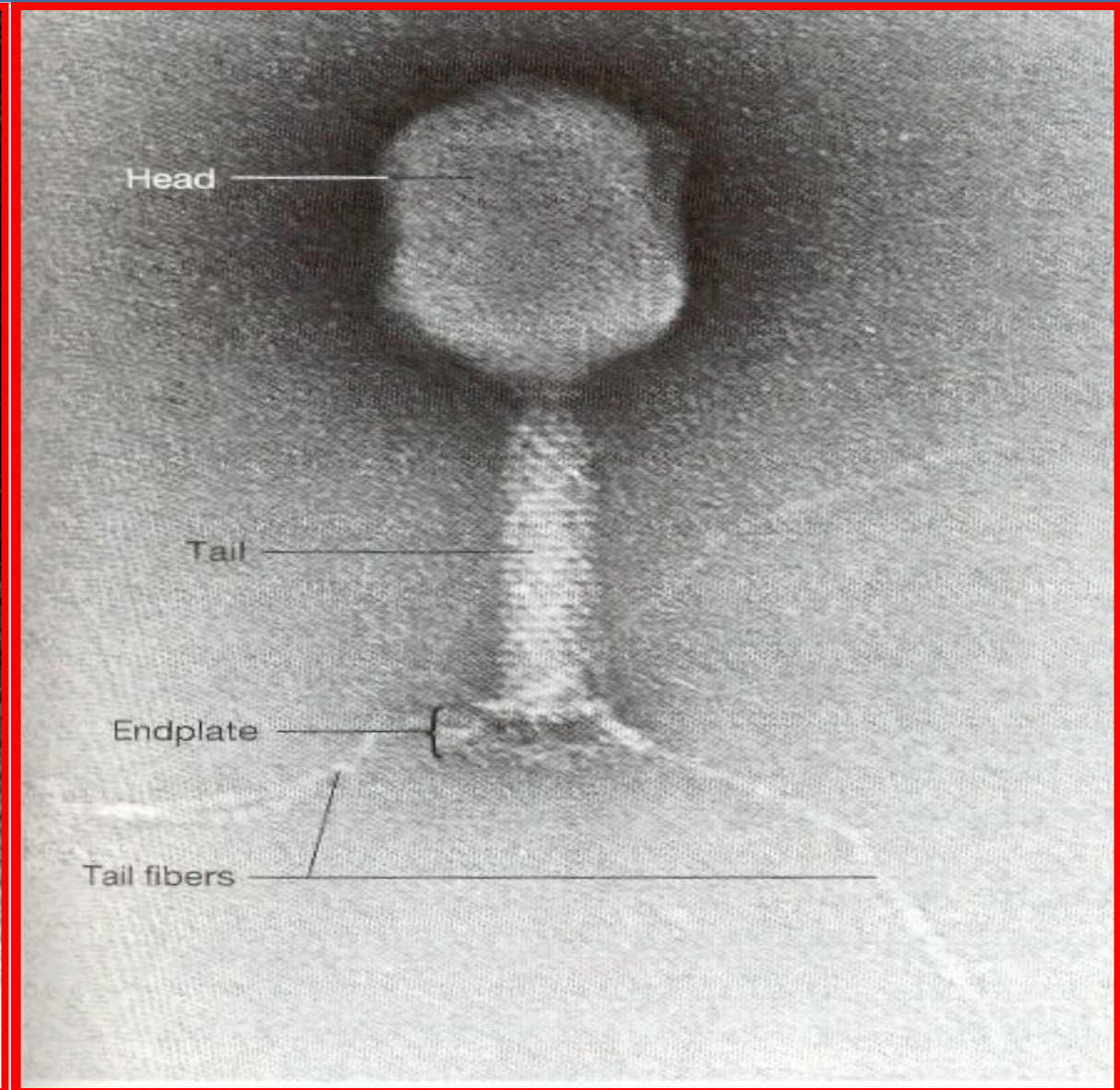
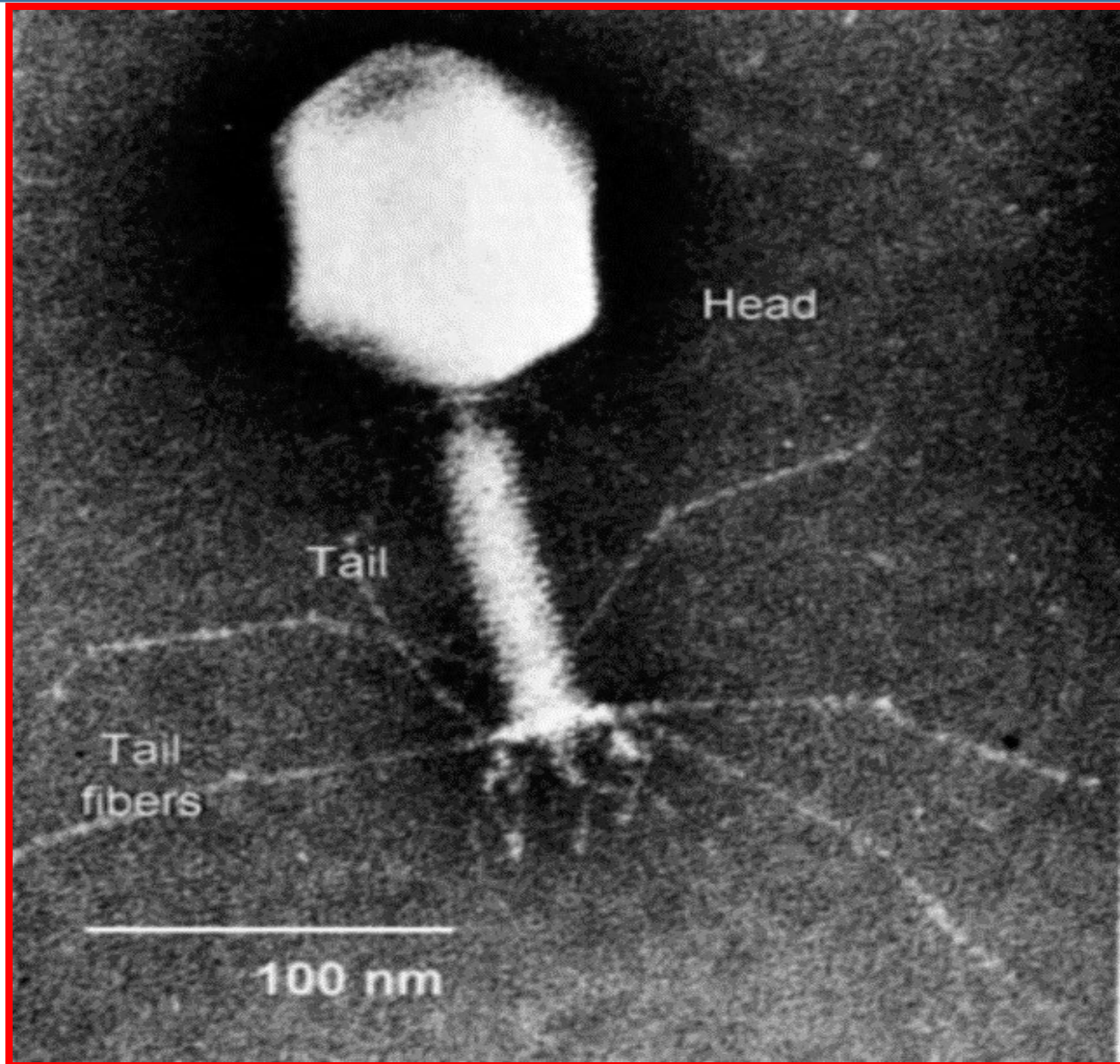
61%



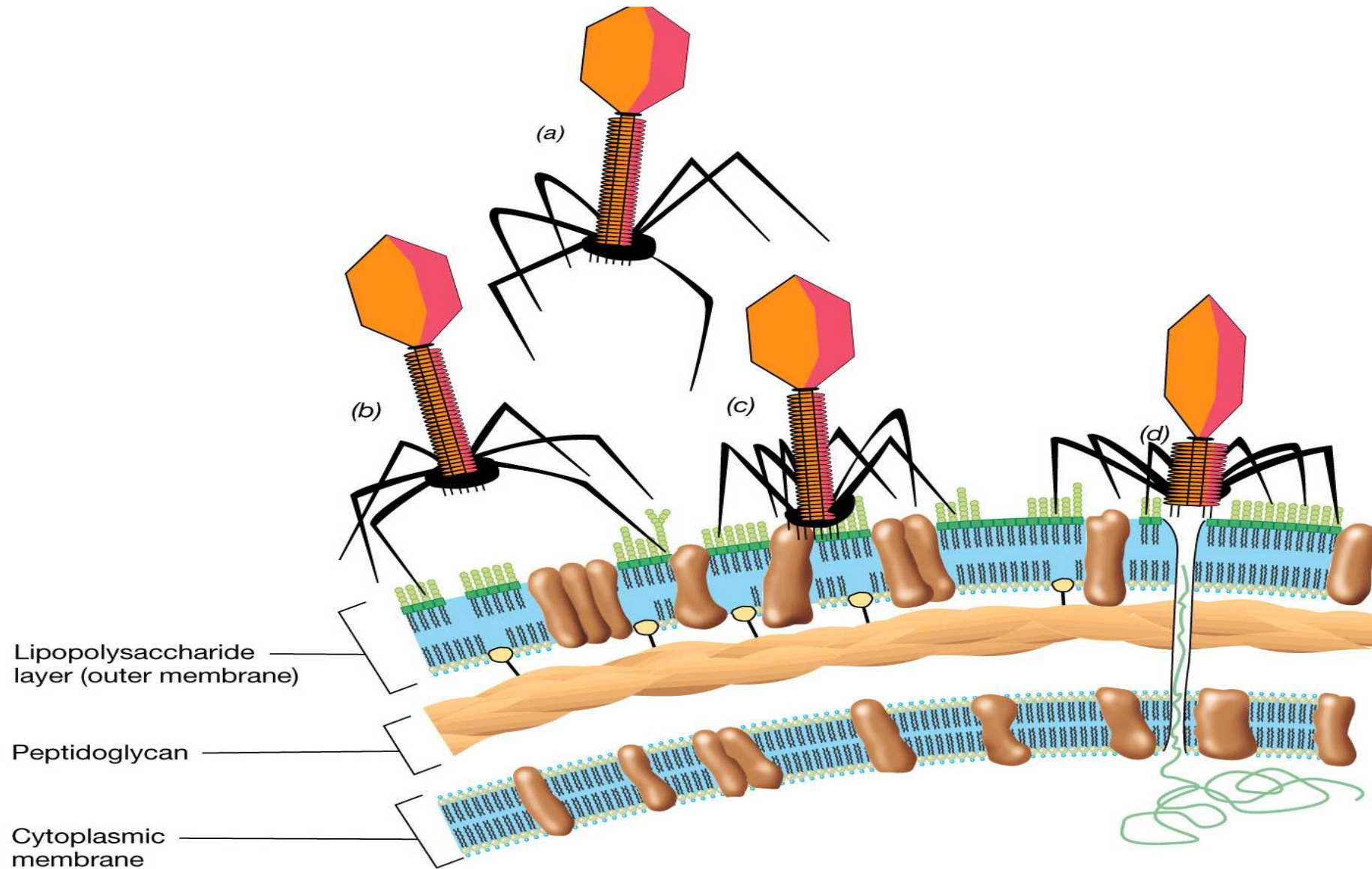
14%

Caudovirales: tailed phages  
n = 5000 = 96% of phages

# *E. coli* phage T4 (Myoviridae)



# Phages: Infection by *E. coli* T4-bacteriophage



# Phages: Life cycles. Chronic, lytic, lysogenic

**Chronic phages** (e.g. *E. coli* phage M13):

after injection phage particles are formed immediately.

These leave the host cell without lysis

**Lytic phages** (e.g. *E. coli* phage T4):

**Therapeutic phages**

after injection phage particles are formed immediately and the

bacterial cell is lysed before duplication: **virulent phages**

**Lysogenic phages** (e.g. *E. coli* phage Lambda):

after injection the phage genome is incorporated into the bacterial genome as a prophage

and duplicated together with the bacterial genome:

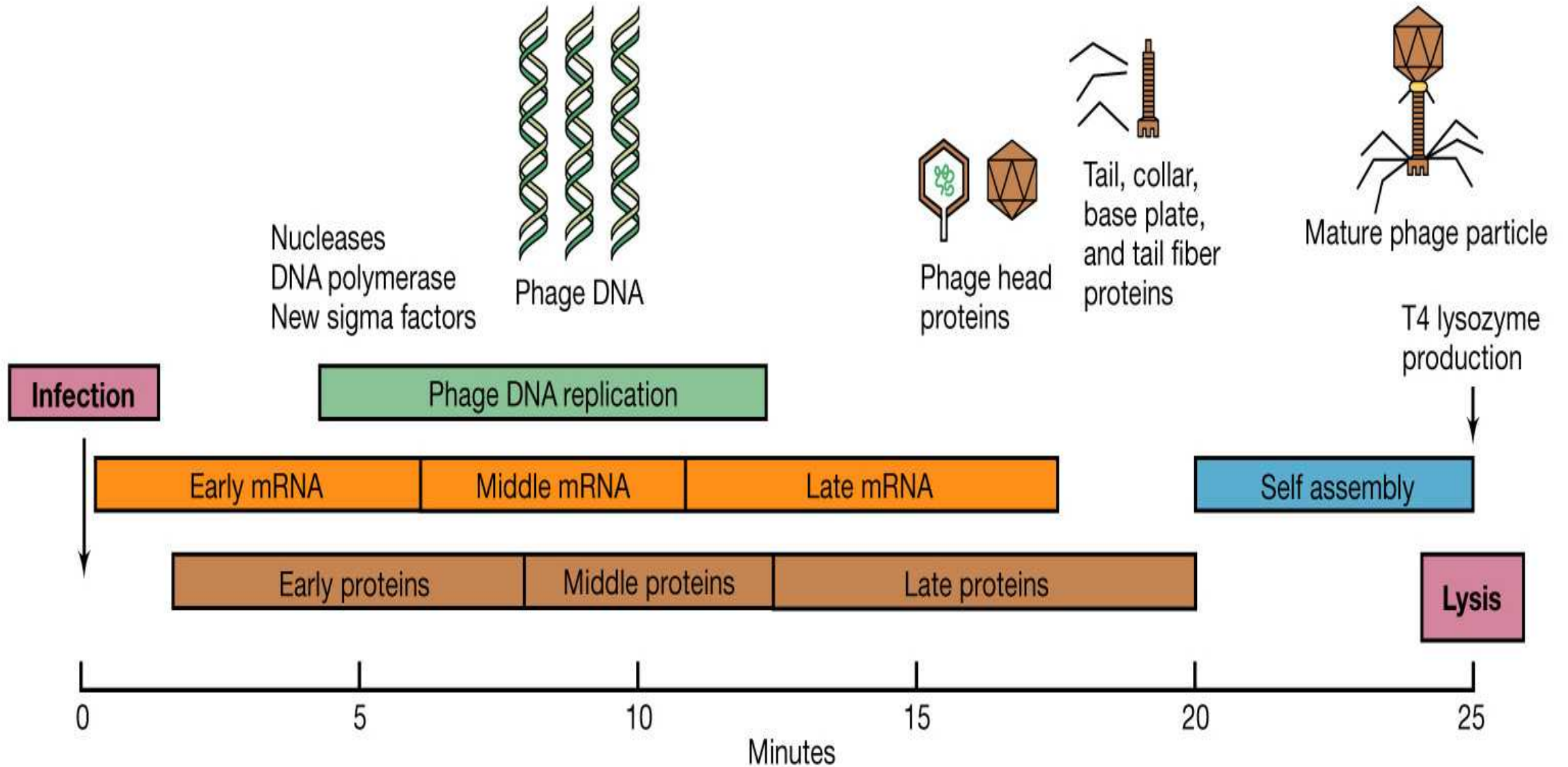
***lysogenic phase***

later the prophage can be activated and enter a lytic cycle:

***lytic phase***

**temperate phages**

# Time course of lytic infection cycle



# Phage therapy: advantages

## Narrow spectrum

- no effect on commensal microflora
- no cross-resistance effects
- flexible: cocktail spectrum can be adapted to the clinical needs  
treatment can be customized/personalized

## Different kinetics

- in theory one single dose can be sufficient to treat an infection
- less dependant on blood stream: phages pass also BBB  
(Dabrowska et al. 2005. Bacteriophage penetration in vertebrates. *J. Appl. Microbiol.* **98**: 7-13.)
- phage transfer to other individuals possible: prophylactic effect

No relation to antibiotic resistance: MDR bacteria can be treated.

# Phage therapy: strategies - 1

## 1. Classic: use of **cocktails of lytic virulent** phages

Merril et al. 2003. The prospect for bacteriophage therapy in Western medicine. **Nature Reviews/Drug Discovery 2**: 489-497.

## 2. Use of **phage-derived antibacterial** products:

T4-lysozyme, lysines, capsule polysaccharide depolymerases, ...

Loeffler et al. 2001. (group of Fischetti, also KULeuven: Volckaert, Lavigne)

Rapid killing of *Streptococcus pneumoniae* with a bacteriophage cell wall hydrolase. **Science 294**: 2170-2172.

Two different lines of reasoning lead to the estimate that 2 billion phage genes are present, i.e. that only 0.0002% of the global phage genome – comprised in 100 million phage species has been sampled.

Rohwer, F. 2003. Global phage diversity. **Cell 113**: 171-182.



# Phage therapy: strategies - 2

## 3. Genetically manipulated lysogenic phages for *in situ* gene delivery:

--> *in situ* delivery to bacterial cells of

- \* killing genes (doc)

- \* antisense RNA to block translation

Westwater et al. 2003. Use of a genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections.

**Antimicrob. Agents Chemother. 47: 1301-1307.**

## 4. Phages as **probiotics with immunomodulatory effects?**

Phages inhibit human T-cell activation and proliferation

Phages diminish cellular infiltration into allogeneic skin allografts

Gorski et al. 2006. Bacteriophages and transplantation tolerance.

**Transplant. Proc. 38: 31-333.**

# Phages: safety. Theoretical considerations - 1

## Phages are safe by definition: viruses which infect bacteria only

1. Bacteriophages infect specifically bacteria since they need to recognize bacterial cell wall structures: *peptidoglycane, LPS*.
2. Bacteriophages that were manipulated genetically to infect mammalian cells were *not able to multiply inside* the mammalian cells after infection.  
Di Giovine *et al.* 2001. Binding properties, cell delivery, and gene transfer of adenoviral penton based displaying bacteriophage. **Virology** **282**: 102-112.
3. *No bacteriophage genes* can be found *in the human genome*, whereas retro-viruses have left hundreds of genes integrated into the human genome.

### *In summary,*

bacteriophages have *no tropism* towards mammalian cells and *cannot multiply* in them.

# Phages: safety. Theoretical considerations - 2

Bacteriophages are numerous and ubiquitous:

## **Numerous**

Estimate of total number of tailed phage particles on Earth:

$4-6 \times 10^{31} = 10\text{-fold of number of prokaryotes.}$

Bergh. 1989. **Nature** **340**: 467-468

Whitamn et al. 1998. **PNAS** **95**: 6578-6583

## **Ubiquitous**

Up to  $\log_9$  phages per ml of surface waters

In animal sera, in vaccines, in food

*E. coli* phages in 11% of faeces of healthy persons

*B. fragilis* phages in 68% of faeces of healthy persons

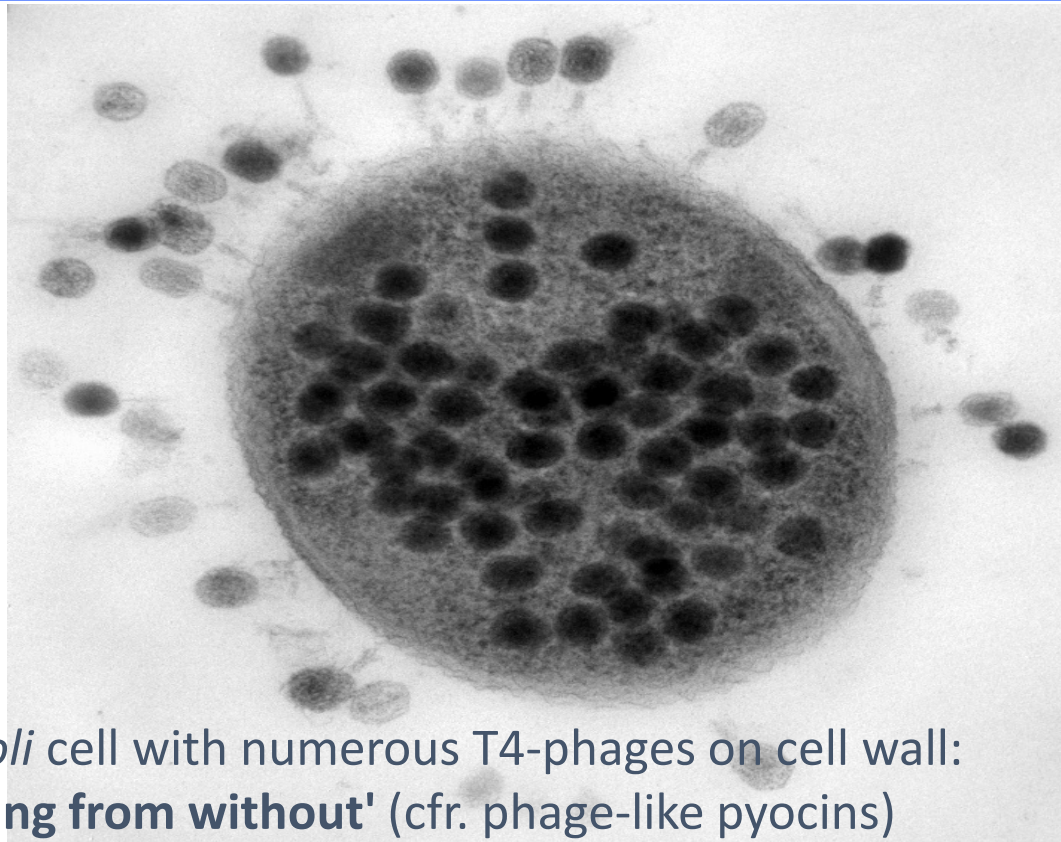
**"We live in a sea of phages"**

still no infections with phages have been reported

# Phage therapy: safety. Lytic vs lysogenic

Use of lytic phages and not lysogenic phages:

3. Lytic phages eradicate bacterial populations more rapidly and completely:  
No lysogenic cycle + 'Killing from without'



*E. coli* cell with numerous T4-phages on cell wall:  
**'Killing from without'** (cfr. phage-like pyocins)

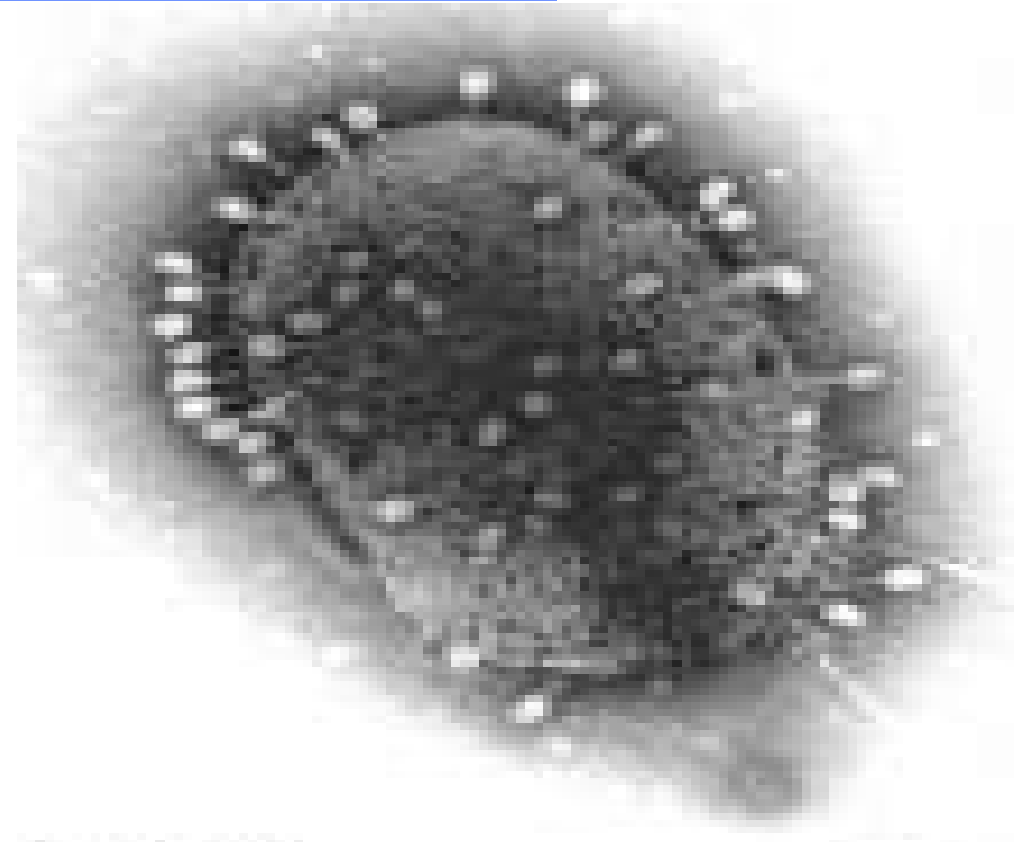


Figure 10.11.11

# Phage therapy: safety in practice

## Animal studies

**Numerous animal experiments** (see efficacy), without adverse effects.

Merril *et al.* (1996) and Capparelli *et al.* (2005) selected bacteriophages for persistence in the mouse circulatory system, indicating that their persistent systemic presence does not pose a problem to mammals.

Merril et al. 1996. Long-circulating bacteriophage as antibacterial agents. **Proc Natl Acad Sci USA 93**: 3188-3192.

Capparelli et al. 2005. Selection of an *Escherichia coli* O157:H7 bacteriophage for persistence in the circulatory system of mice infected experimentally. **Clin. Microbiol. Infection 12**: 248-253.

# Phage therapy: Problem 1

## Narrow spectrum

Advantage: commensal microflora not affected

Disadvantage: species and clone need to be identified before application.

Solutions:

1. Use of phage mixtures (cocktails)
2. Application in chronic infections: time to select appropriate phages
3. Broad spectrum phages (e.g. all *S. aureus*) exist.
- (4. Add phages to antibiotics)

# Phage therapy: Problem 2

## Bacterial resistance

### Most important strategies of bacteria for developing phage resistance:

1. Mutation of cell wall receptors which are used by phages as adherence ligand
2. DNA restriction/modification systems: nonmodified (phage) DNA is restricted.

Mutant bacteria can become susceptible for other phages.

Mutant bacteria can lose virulence.

*E. coli* K1-phages induce phage-resistant *E. coli*

but these are K1 negative: **reduced virulence** (Smith & Huggins 1982).

Phages can co-evolve (they do since 4 billion years).

Phages can be propagated in vivo to adapt to resistant hosts.

New phages can be found: fishing for phages.

# Phage therapy: Problem 3

## Can phages penetrate biofilms?

Hanlon *et al.* 2001. **Reduction in exopolysaccharide viscosity** as an aid to bacteriophage penetration through *Pseudomonas aeruginosa* biofilms. **Appl. Environ. Microbiol.** 67: 2746-2753.

Sillankorva *et al.* 2004. *Pseudomonas fluorescens* infection by bacteriophage PhiS1: the influence of temperature, host growth phase and media. **FEMS Microbiol. Lett.** 241: 13-20.

**85% biomass reduction** in planktonic as well as biofilm growth.

Hughes *et al.* 1998. Biofilm susceptibility to bacteriophage attack: the role of phage-borne **polysaccharide depolymerase**. **Microbiology** 144: 3039-3047.





# The Sleeping Giant

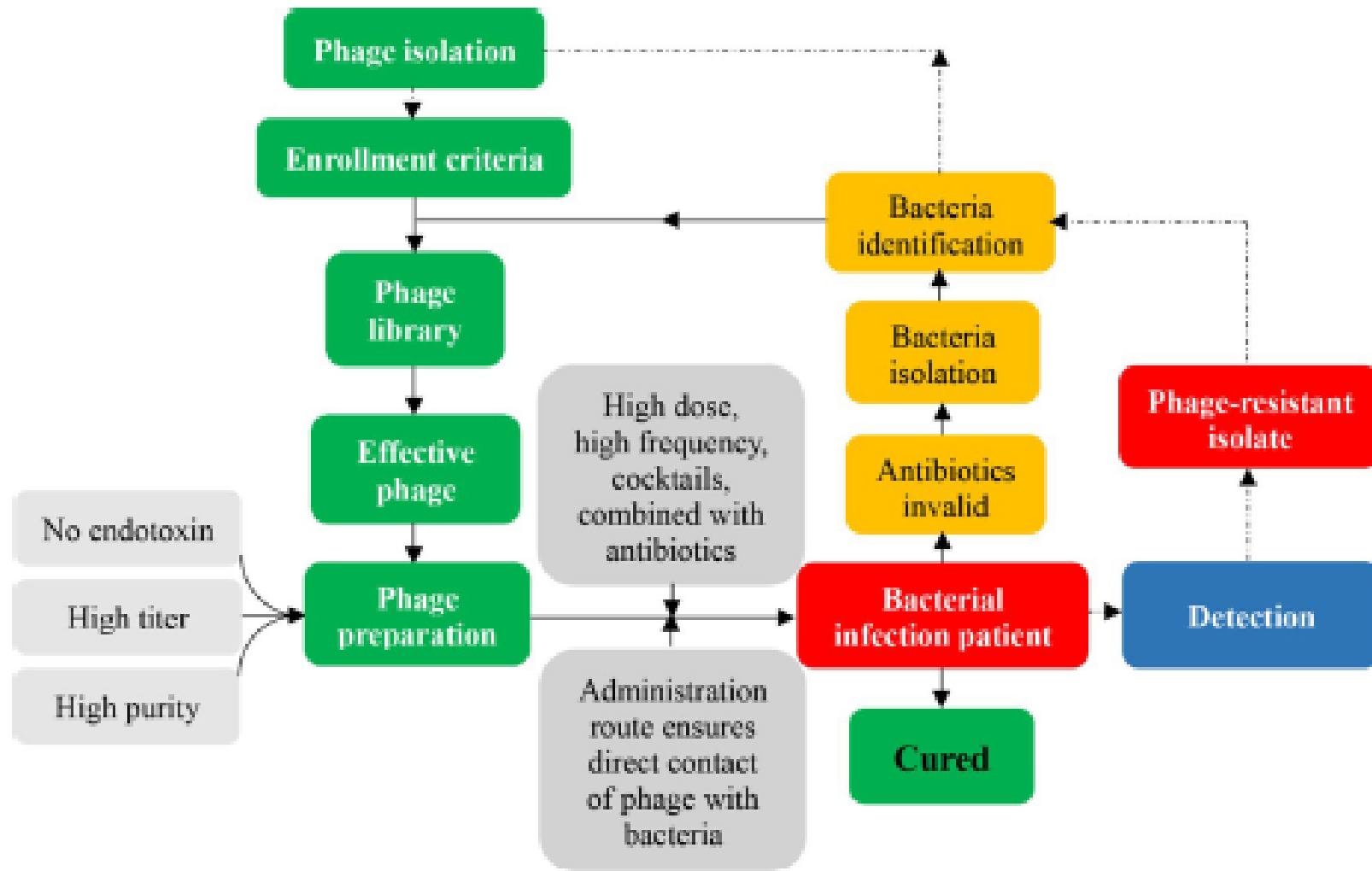
# Bacteriophage application in different fields

- Urology and Gynecology ( Prostatitis, urethritis, vaginitis, cystitis etc)
- Surgical infections (chronic wounds, diabetic ulcers, prosthetic foot ulcers)
- Internal medicine, ENT, Pediatrics (Gastrointestinal tract disease, respiratory system diseases, cystic fibrosis, skin and tissue disease)
  
- There are several clinical trials going on
- The first Phage therapy center in the US (San Diego)
- Global recognition is increasing

# Pharmaceutical preparations used for clinical treatment

SES Batteriofago	Staphylococcus, E.coli, Streptococcus
Fersis Batteriofago	Staphylococcus, Streptococcus
ENCOfago	Shigella, Salmonella, E.coli , Staphylococcus
Intesti Batteriofago	Shigella, Salmonella, Staphylococcus spp., Proteus, E.coli, Pseudomonas aeruginosa, Enterococcus faecalis
Pyo Batteriofago	Staphylococcus, E.coli, Streptococcus, Pseudomonas, Proteus
Staphylofago	Staphylococcus spp.
“Preparazioni di Fagi individuali”	



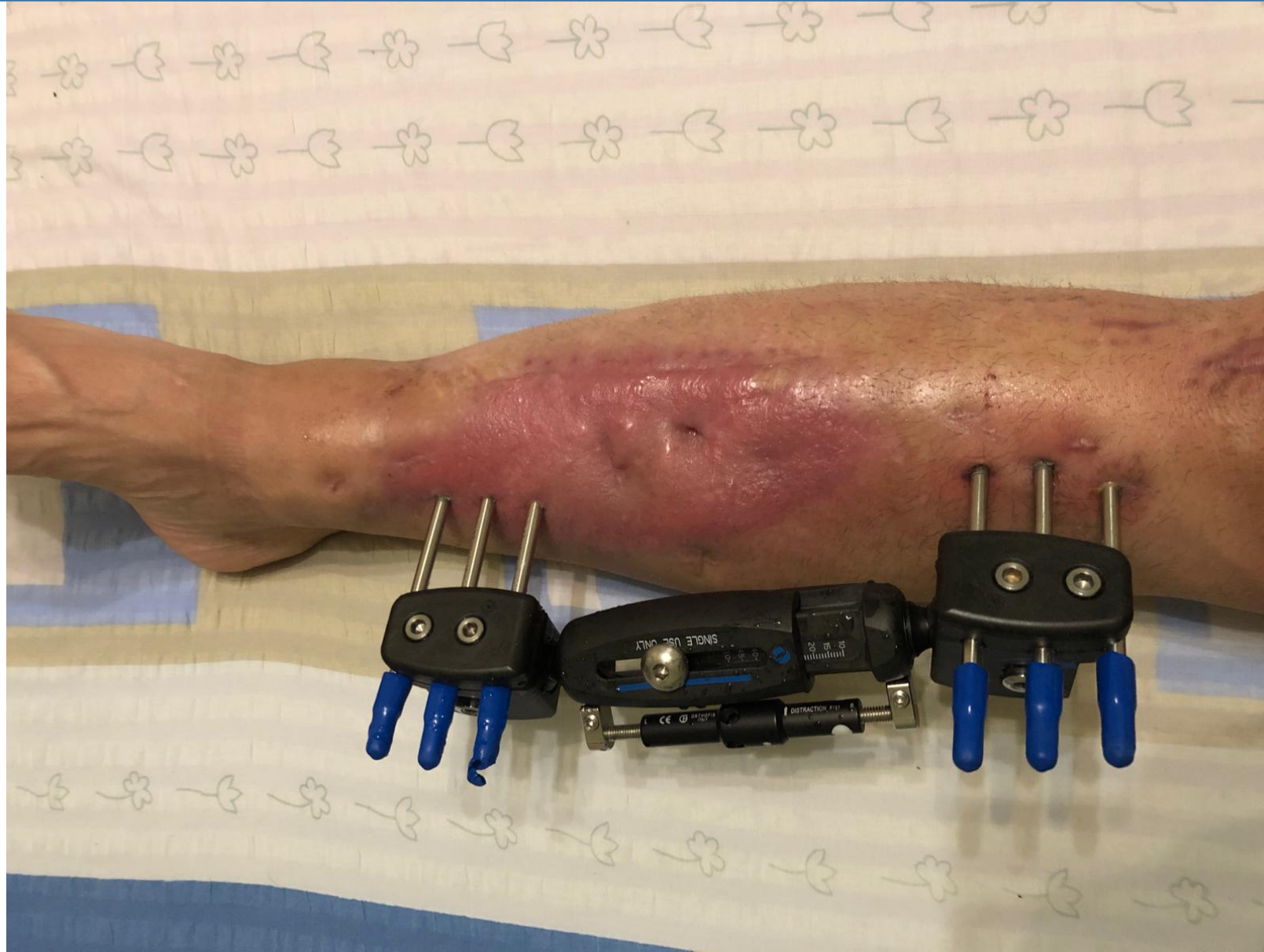


**Fig. 1** The Whole Streamlined Procedure of Phage Therapy in Clinical Practice. The criteria for enrolling phages for therapy should be established, and a library containing different phages should be established in advance. Antibiotic drugs should be proven ineffective for treatment of the bacterial infection, and the pathogen should be isolated and identified for further use in screening its corresponding effective phage in the library. Phage preparations that are free of endotoxin with a high titer and high purity should be generated. Administration strategies, including high dose, high frequency, cocktails, and combination with antibiotics, should be prioritized. The administration route should ensure direct contact of the phage with bacterium. The emergence of phage-resistant isolates and improvement of the infection should be monitored in a timely manner

# A clinical case in Italy – 1

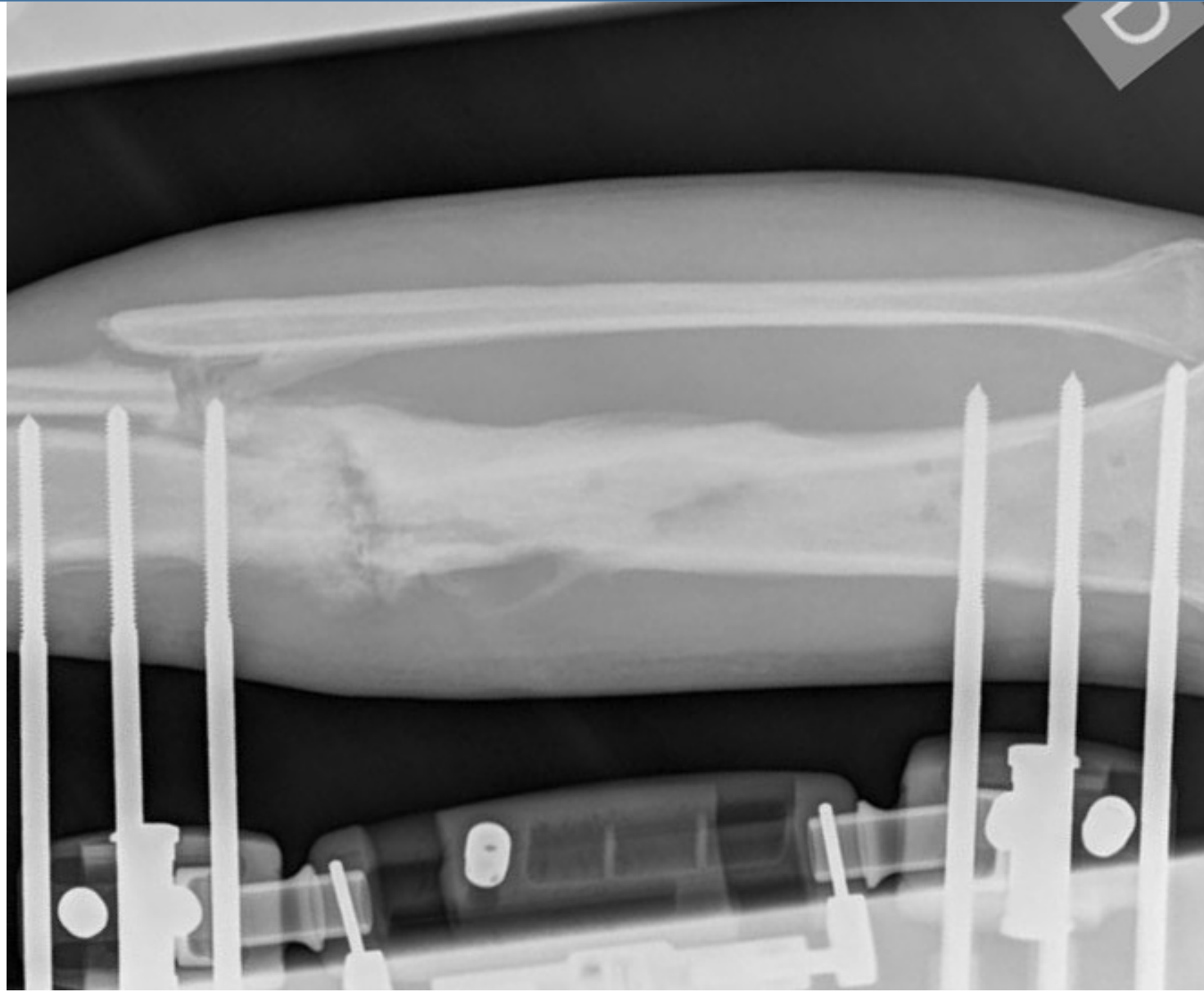
## Leg Pseudomonas osteomyelitis after exposed fracture

43 yrs old man.  
Clinical picture  
after several  
operation  
performed on  
the infected leg.  
**Before the cure  
with  
bacteriophages**



## A clinical case in Italy - 2

The fistula healed after 10 days. The X-ray taken after 40 days show the formation of new bone



# A clinical case in Italy - 3

Clinical picture after 3 months of therapy. The external fixators were removed. The patient can walk without any help or device.





EVOLUTION,  
MEDICINE, &  
PUBLIC HEALTH

# Phage treatment of an aortic graft infected with *Pseudomonas aeruginosa*

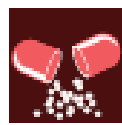
Benjamin K. Chan,<sup>1</sup> Paul E. Turner,<sup>1,2</sup> Samuel Kim,<sup>3</sup> Hamid R. Mojibian,<sup>4</sup> John A. Elefteriades<sup>5</sup> and Deepak Narayan<sup>\*,3</sup>

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Case Report

# Bacteriophage Therapy for Critical Infections Related to Cardiothoracic Surgery

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<sup>6</sup> Clinical Research Group (KFO 311), German Research Foundation, 30625 Hannover, Germany

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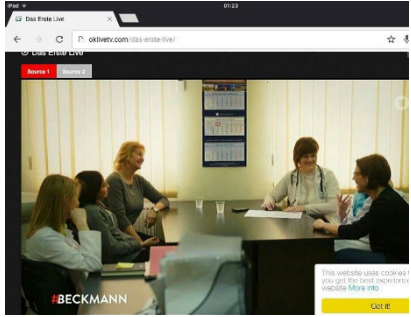
† These authors contributed equally to this work.

# Our patients around the world



# Media Exposure

Beckmann,  
German TV



Dutch- Zorg



French TV-5,  
French Radio



VICE, Motherboard (US, Holland)



Phages offers virus alternative to antibiotics  
Reuters 842 views

Reuters



BBC -2



Norwegian TV



*Antico Forno Nonna Esterina*

*Nenti social...  
sulu cu prova  
torna!!!*

# **Bacteriophage therapy: an overview and the position of Italian Society of Infectious and Tropical Diseases**

**Novella Cesta<sup>1</sup>, Mariagrazia Di Luca<sup>2</sup>, Mario Corbellino<sup>3</sup>, Marcello Tavio<sup>4</sup>,  
Massimo Galli<sup>3,5</sup>, Massimo Andreoni<sup>6</sup>**

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<sup>6</sup>Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy; Infectious Diseases Clinic, University Hospital "Tor Vergata", Rome, Italy

## Eradication of a Multidrug-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae* Isolate Following Oral and Intra-rectal Therapy With a Custom Made, Lytic Bacteriophage Preparation

Mario Corbellino,<sup>1,✉</sup> Nicolas Kieffer,<sup>2</sup> Mzia Kutateladze,<sup>3</sup> Nana Balarjishvili,<sup>3</sup> Lika Leshkasheli,<sup>3</sup> Lia Askilashvili,<sup>3</sup> George Tsertsvadze,<sup>3</sup> Sara Giordana Rimoldi,<sup>4</sup> Deia Nizharadze,<sup>5</sup> Naomi Hoyle,<sup>5</sup> Lia Nadareishvili,<sup>5</sup> Spinello Antinori,<sup>1,6</sup> Cristina Pagani,<sup>4</sup> Daniele Giuseppe Scorza,<sup>4</sup> Ai Ling Loredana Romanò,<sup>7</sup> Sandro Ardizzone,<sup>6,8</sup> Pierngiorgio Danelli,<sup>6,9</sup> Maria Rita Gismondo,<sup>4,6</sup> Massimo Galli,<sup>1,6</sup> Patrice Nordmann,<sup>2</sup> and Laurent Poirel<sup>2</sup>

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antimicrobial resistance who were without a history of contact with medical care while abroad, with a demonstrated length of carriage of at least 6 months [4–6].

Besides the use of antibiotics, alternatives are urgently needed to significantly contribute to the eradication of MDR bacteria in general, and CP Gram-negative bacteria in particular. Among those alternative strategies, the use of phage therapy is currently being reconsidered for treating corresponding infections. Custom-made bacteriophage therapy (BT) consists of the clinical use of viruses that have been preliminarily selected *in vitro* for their specific and strictly lytic activity against a bacterial pathogen isolated in culture, with the aim of treating the infection sustained by the pathogen [7]. Several examples of the successful treatment of infections caused by MDR bacteria have been reported [7–9]. However, to the best of our knowledge, although it has been suggested [10], no gut decolonization strategy using bacteriophages has been reported to date.

We describe herein a patient for whom custom-made BT was



## HHS Public Access

Author manuscript

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### Early clinical experience of bacteriophage therapy in three lung transplant recipients

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<sup>3</sup>Department of Infectious Diseases, Cleveland Clinic Foundation, Cleveland, OH

<sup>4</sup>AmpliPhi Biosciences, San Diego, CA

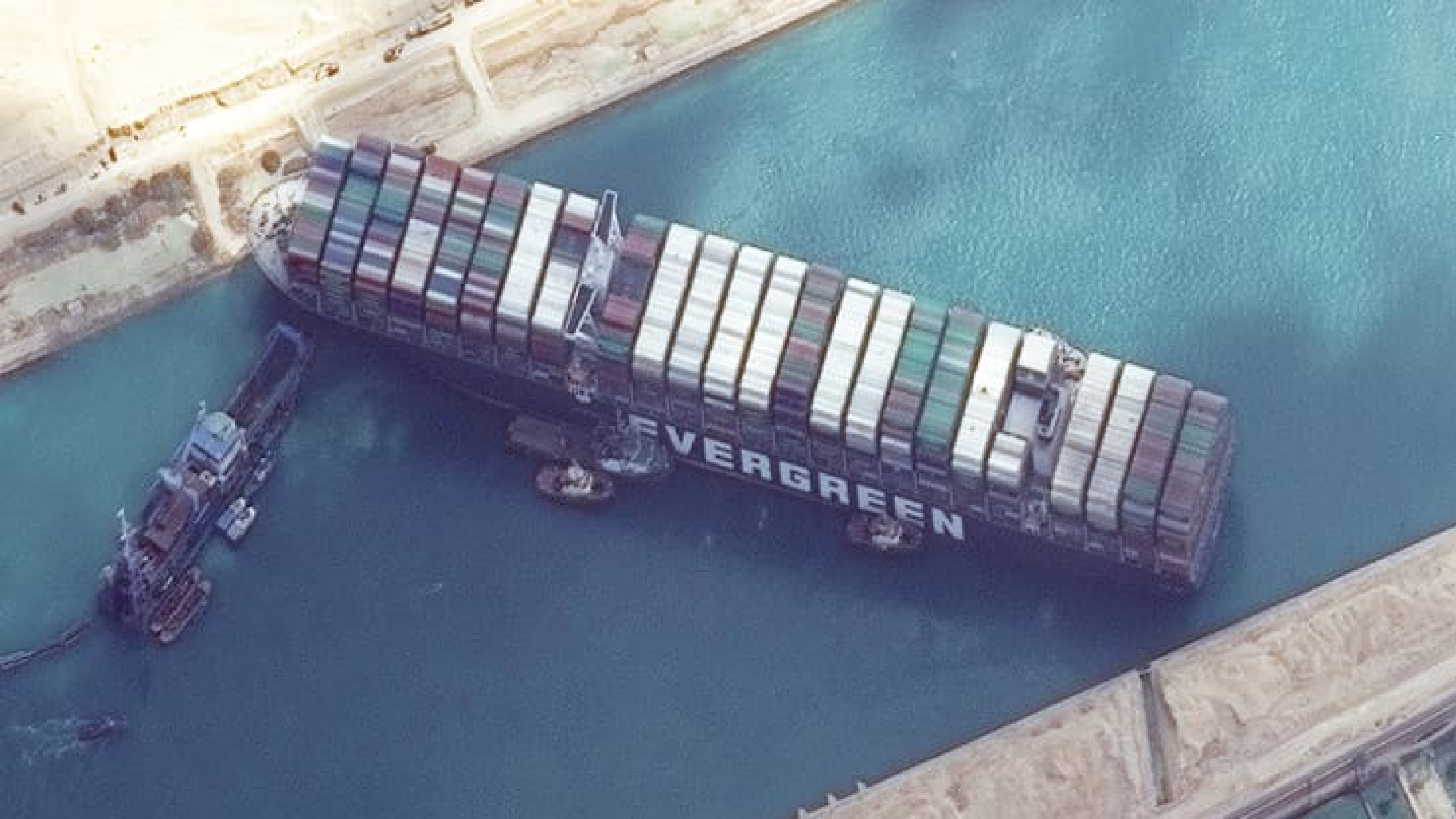
<sup>5</sup>Adaptive Phage Therapeutics, Gaithersburg, MD

<sup>6</sup>Naval Medical Research Center, Biological Defense Research Directorate, Fort Detrick, MD

<sup>7</sup>Division of Pulmonary, Critical Care & Sleep Medicine, University of California San Diego, La Jolla, CA

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<sup>9</sup>Division of Infectious Diseases, University of Pennsylvania, Philadelphia PA





# Helsinki Declaration

- *In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.*
- *Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy.*
- *In all cases, new information should be recorded and, where appropriate, published.*
- *The other relevant guidelines of this Declaration should be followed.*

# Randomized Open Label, Parallel Group, Controlled Study to Evaluate the Safety and operative procedures Sparing Effect of Phage Therapy With Antibiotics for Patients with recurrent cholangitis

## Study Description

- Brief Summary:
- This is a study designed to evaluate bacteriophage therapy in patients with recurrent cholangitis in PTBD carriers.

## Condition or disease

- **Intervention/treatment Phase**
- Recurrent Cholangitis
- Biological: Phage Therapy Procedure , antibiotics:
- Phase 1Phase 2

## Detailed Description:

- This is a study designed to evaluate bacteriophage therapy in immunosuppressed patients with recurrent cholangitis and PTBD carriers, caused by the following organisms: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus sp., Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella or pneumonia or other bacteria sensitive to available preparations of phages cocktails.
- This study will also compare the safety and efficacy of phage therapy in conjunction with antibiotics versus standard of care (SOC) antibiotics only.

- **Outcome Measures**

- **Primary Outcome Measures :**

- Safety and tolerability of phage therapy [ Time Frame: Day 1 through Week 26 ]
- Incidence and type of adverse events

- **Secondary Outcome Measures :**

- Efficacy of phage therapy to prevent cholangitis and the need for interventional radiology procedures in patients carriers of PTBD with recurrent cholangitis . [ Time Frame: 6 weeks after completion of phage therapy ]
- Proportion of phage-treated patients with no need for repeated interventional radiology and no evidence of bile duct infection.
- Efficacy of phage therapy to improve quality of life as assessed by outcome questionnaire. [ Time Frame: Week 26 ]
- Time to reach minimum clinically important difference in dysfunction and outcome indicators.
- Incidence of recurrent postoperative infection from the preoperative isolated bacterial strain



# Phage therapy: Summary

Phages are everywhere:

The world is a phage. We live in a sea of phages.

Different strategies are possible:

lytic phages

lytic phage products

modified lysogenic phages for gene delivery

phages as probiotics?

Phages are safe

Phages are efficient, also

against antibiotic resistant bacteria and  
against bacteria in biofilm

Clinical trials are held back because of 'safety' considerations and lack of appropriate regulatory framework

<https://www.phages.healthcare/>  
[alfonso.recordare@phages.healthcare](mailto:alfonso.recordare@phages.healthcare)







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# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

**Prof. Antonio Crucitti**

**Direttore U.O.C. Chirurgia Generale e Mininvasiva**

**Osp. Generale Cristo Re**

**Università Cattolica del S. Cuore - Roma**







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*e-mail: xeniaeventi@gmail.com*

## Il sottoscritto

ai sensi dell'art. 76 comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e in accordo con il Codice Etico della Xenia S.a.s.

dichiara

per l'evento in oggetto l'esistenza negli ultimi due anni di rapporti di natura finanziaria e lavorativa con le seguenti imprese commerciali operanti in ambito sanitario

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



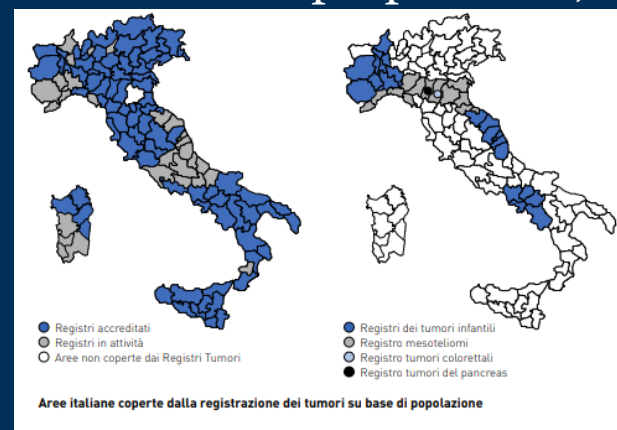
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## Dimensioni del problema



In Italia, sulla popolazione totale, il tumore del colon-retto è il secondo più frequentemente diagnosticato con 43.702 casi stimati nel 2020 pari all'11,6% di tutti i tumori, preceduto solo dal tumore della mammella.

In base ai dati ISS (AIRTUM 2020) si calcola che 1 uomo ogni 12 ed una donna ogni 19 aa. svilupperanno un tumore del colon retto nell'arco della propria vita, verosimilmente entro gli 84 anni.



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Dimensioni del problema



Il cancro colo-rettale risulta al secondo posto in quanto a mortalità tra tutti i tumori dopo quello del polmone, con una proporzione del 10,8% sul totale dei decessi oncologici (ISTAT 2017).



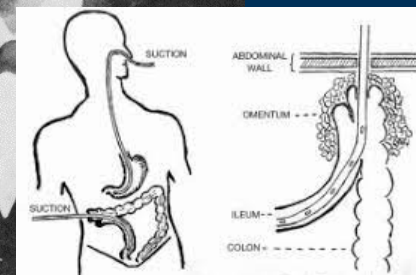
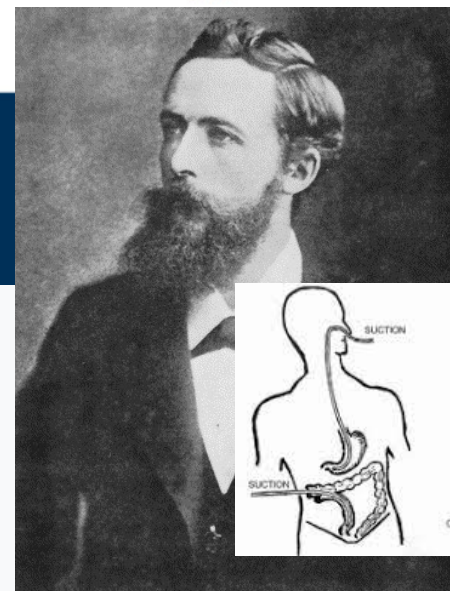
COLON RETTO	
Incidenza	Nel 2020, sono attese circa 43.700 nuove diagnosi (maschi = 23.400; femmine = 20.300)
Mortalità	Nel 2020, sono stimati 21.600 decessi (maschi = 11.300; femmine = 10.300).
Sopravvivenza netta a 5 anni dalla diagnosi	65% in entrambi i sessi
Sopravvivenza di ulteriori 5 anni condizionata ad aver superato il primo anno dopo la diagnosi	76% nei maschi e 77% nelle femmine
Prevalenza	Sono 513.500 le persone viventi in Italia dopo una diagnosi di tumore del colon retto (maschi = 280.300; femmine = 233.200)

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Chirurgia colo-rettale



Nel 1823, un praticante di nome Reybard fu accreditato di aver eseguito la prima resezione del colon.

Da allora abbiamo assistito a grandi progressi nella chirurgia del cancro del colon; basato su una migliore comprensione della malattia e del suo comportamento e sui numerosi progressi in tecniche chirurgiche sicure e innovative da parte di chirurghi pionieri.

- La chirurgia continua ad essere il trattamento con maggiori probabilità di curare il cancro del colon-retto.
- Diversi approcci chirurgici a seconda della posizione, colon o retto, dello stadio e delle dimensioni del tumore o se il tumore è metastatico.
- Altre opzioni di trattamento includono radioterapia e chemioterapia da sole o in combinazione.

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Dalla chirurgia a cielo aperto al «buco della serratura»: la laparoscopia

La forma più tradizionale di chirurgia del cancro del colon è nota come «colectomia»

- un'unica lunga incisione nell'addome
- per molti anni (?) è rimasto il cardine

Alla fine del 20° secolo nasce la chirurgia coloretale mininvasiva o laparoscopica (**keyhole surgery**)

- molte incisioni più piccole
- strumenti speciali
- una minuscola videocamera per vedere il colon

Le colonne laparoscopiche di oggi sono molto performanti ed hanno abbattuto i bias che potevano avere quelle di prima generazione

- monitor sempre più grandi
- touch-screen
- riscaldano il gas e riducono l'appannamento delle lenti
- riducono al minimo le % di CO<sub>2</sub> (vantaggi per il tasso di CO<sub>2</sub> ematico)
- 3 o 4 HD, 3D....
- telecamere autofocus e utilizzabili con i coloranti vitali (ICG-verde indocianina)
- grandi memorie per le riprese video .....



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## Dalla chirurgia a cielo aperto al «buco della serratura»: la laparoscopia



La **chirurgia laparoscopica** per il trattamento chirurgico dei tumori colo-rettali è patrimonio di molti centri  
I vantaggi della chirurgia laparoscopica:

- ridotte perdite di sangue
- incisioni più piccole
- minor trauma e minor dolore minor infezioni minor laparoceli
- tempi di recupero ridotti
- più rapido ripristino della funzionalità intestinale
- degenze ridotte
- aspetti immunitari/oncologici

**....non significa che sia l'opzione giusta per tutti, la decisione dovrebbe essere presa dopo una discussione informata tra il paziente e il chirurgo!!!**



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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Dalla chirurgia a cielo aperto al  
«buco della serratura»: la laparoscopia

...ma è proprio vero ?

Medicina scienza e ricerca

## Chirurgia laparoscopica: Italia ancora in ritardo nel trattamento del carcinoma del colon retto

Clinici e istituzioni si confrontano venerdì 23 ottobre a Milano nella tavola rotonda "Chirurgia laparoscopica del colon retto: il paradosso Italia" all'interno del 117° Congresso Nazionale della Società Italiana di Chirurgia

di Redazione Aboutpharma Online

| 21 Ottobre 2015



Un paradosso tutto italiano. È la situazione della chirurgia laparoscopica del colon retto nel nostro paese. Pur annoverando a livello nazionale strutture cliniche all'avanguardia in grado di essere benchmark virtuosi sia in termini di qualità delle cure che di ottimizzazione dell'uso delle risorse economiche, la tecnica non è ancora diffusa in Italia come in altri paesi occidentali. Una sfida ancora oggi da affrontare per consentire al BelPaese di raggiungere i livelli delle altre nazioni europee nel trattamento mininvasivo del carcinoma del colon retto, il tumore a maggiore insorgenza nella popolazione italiana.

.....raccomandazioni dedicate al corretto utilizzo delle tecniche laparoscopiche

nella chirurgia coloretale, che in Italia non supera il **29%. (2020)**

L'obiettivo è promuovere una corretta formazione dei chirurghi e di conseguenza implementare le loro abilità nell'utilizzo di queste tecniche.



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica



La chirurgia robotica è un'altra forma di chirurgia coloretale minimamente invasiva:

- robot è controllato dal chirurgo tramite una console (comfort)
- maggiore visibilità (3D)
- un computer fornisce precisione e minimo trauma tissutale (nervi...)
- gamma di movimento più precisa rispetto alla mano e al polso umani
- movimento del polso un'articolazione in più della mano umana (wrist)
- minor tasso di complicazioni e infezioni
- più rapido recupero postoperatorio
- riduce significativamente degenza ospedaliera





# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica



Il primo robot chirurgico **ZEUS robotic surgical system (ZRSS)**, sviluppato e prodotto dalla statunitense Computer Motion fu approvato dalla FDA nel 2001.

Il predecessore di tale sistema, chiamato AESOP, fu approvato dalla Food and Drug Administration nel 1994 per assistere i chirurghi nella chirurgia mininvasiva.

Il sistema ZEUS fu cessato nella produzione nel 2003, a seguito della fusione della società produttrice Computer Motion con la sua rivale **Intuitive Surgical**



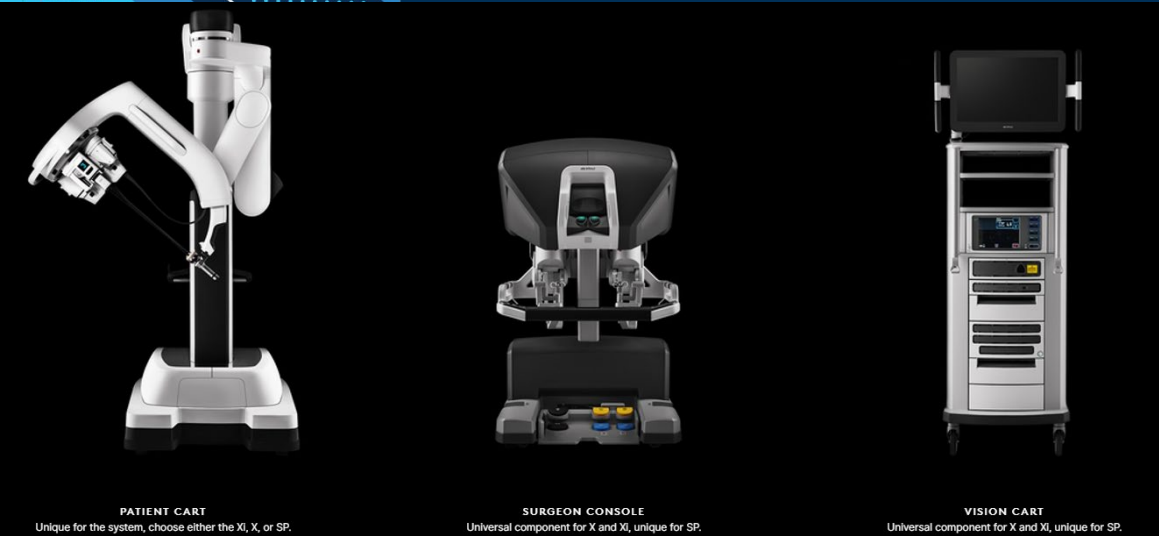
# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: DA VINCI

- Il sistema chirurgico da Vinci, in onore a Leonardo da Vinci, fu messo a punto nella Silicon Valley dalla Intuitive Surgical, e nel 2000 ha ottenuto l'autorizzazione dall'FDA per l'utilizzo in chirurgia laparoscopica.



21 anni, quarta generazione, oltre 8,5 milioni di interventi chirurgici, leader nella robotica chirurgica, al 31.12.19, Intuitive Surgical ha installato 5.582 sistemi da Vinci, 3.531 negli U.S.A., 977 in Europa, **(111 in Italia/22 in Lombardia)**, 780 in Asia e 294 nel resto del mondo, aumentando l'adozione della chirurgia mininvasiva, in un'ampia gamma di procedure chirurgiche con configurazioni flessibili, architettura aggiornabile, interfaccia coerente, ampia dotazione di strumenti

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: DA VINCI

Il chirurgo, seduto in console, manovra a distanza quattro bracci robotici che migliorano i gesti umani, eliminandone il fisiologico tremore e garantendo una visione 3D e immersiva del campo operatorio, con la possibilità di raggiungere aree anatomiche difficili anche con un unico accesso

Diverse specialità:

- urologia
- chirurgia generale
- ginecologia
- chirurgia toracica
- cardiocirurgia
- chirurgia pediatria
- otorinolaringoiatria
- chirurgia dei trapianti



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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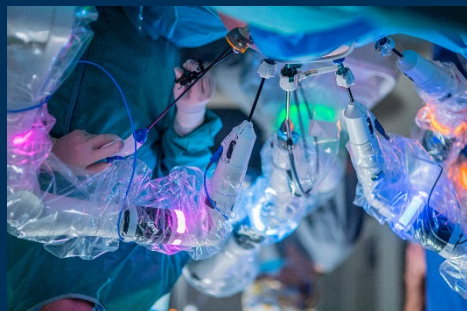
## La chirurgia robotica: VERSIUS

8 aprile 2022  
9 aprile 2022

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TUMORI DELL'APPARATO DIGERENTE  
Presidenti: Gianluigi Greco e Bruno Nardo

PRESENTED BY UNIVERSITÀ CATTOLICA DEL SACRO CUORE

XENIA



2014	2016	2017	2018	2019	2020	2021
<p><b>January 2014:</b> Company was founded with the purpose of transforming surgery for millions of people.</p> <p><b>July 2014:</b> The CMR Surgical version of the Palo Alto garage is created. The CMR Surgical "barns" become home to the development of Versius.</p>	<p><b>June 2016:</b> First series of cadaveric trials completed.</p>	<p><b>December 2017:</b> CMR Surgical named one of the UK's top 10 business disruptors to watch &amp; one of the year's 'Fierce 15'.</p>	<p><b>June 2018:</b> CMR Surgical closes Series B funding round, raising \$100 million – Europe's largest funding round in the medical technology sector.</p> <p><b>September 2018:</b> Versius is introduced to the world for the first time.</p> <p><b>December 2018:</b> CMR Surgical named Britain's sixth-fastest growing business.</p> <p><b>December 2018:</b> CMR Surgical launches partnership with Florida Hospital's Nicholson Center to launch the first Versius training programme in the US.</p>	<p><b>May 2019:</b> Company announces successful completion of first 30 in-human surgical procedures using Versius.</p> <p><b>September 2019:</b> CMR Surgical raises \$240 million in Series C funding – Breaking our own record for Europe's largest private financing round in the medical technology sector.</p> <p><b>October 2019:</b> CMR Surgical announces the first commercial introduction of Versius at Galaxy Care Hospital in Pune, India.</p>	<p><b>January 2020:</b> Per Vegard Nerseth is appointed as Chief Executive Officer.</p> <p><b>February 2020:</b> CMR Surgical announces the introduction of Versius into the NHS at NHS Lothian and Milton Keynes University Hospital.</p> <p><b>June 2020:</b> CMR appoints former SpaceX Senior Director, Barrington D'Arcy as Chief Operations Officer.</p> <p><b>September 2020:</b> CMR launches Versius in France as it extends global footprint.</p> <p><b>November 2020:</b> Over 1,000 surgeries completed using Versius.</p>	<p><b>February 2021:</b> CMR announces the introduction of Versius into leading surgical robotics markets Australia and Germany.</p> <p><b>June 2021:</b> CMR Surgical becomes the Official Medical Devices Partner of ParalympicsGB.</p> <p><b>June 2021:</b> CMR Surgical raises \$600 million in Series D financing, the largest ever private MedTech raise.</p>

- Sistema Versius su base digitale, modulare, compatto e con singoli bracci robotici compatibili per dimensioni con qualsiasi sala operatoria
- specialità: Chirurgia Generale, Ginecologia, Urologia e Chirurgia Toracica
- interventi di laparoscopia avanzata
- strumenti completamente articolati
- sistema di visione 3D full HD 3D HD,
- comandi posizionati su una console ergonomica

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: VERSIUS

The Versius System



Open and ergonomic  
console

All functions on the hand  
controllers



Modular and  
collaborative arms

Enabled by the unique  
V-Wrist



Enhanced dexterity  
and control

With fully wristed  
instruments



Clear vision and  
depth perception

3D HD vision

- sistema modulare
- bracci robotici indipendenti tra loro, liberi intorno al letto operatorio
- disposizione dei trocar tipica delle procedure laparoscopiche
- set-up clinico facilitato
- approccio di tipo “ibrido” alla procedura (robotica/mininvasiva tradizionale),
- utilizzo alternato di strumenti mininvasivi tradizionali e robotici
- massimizzazione di valore
- ottimizzazione dei tempi e dei costi
- utilizzo del sistema robotico anche per l'intero intervento



8 aprile 2022  
 9 aprile 2022

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*Presidenti: Giangiugli Greco e Bruno Nardo*

VENIA

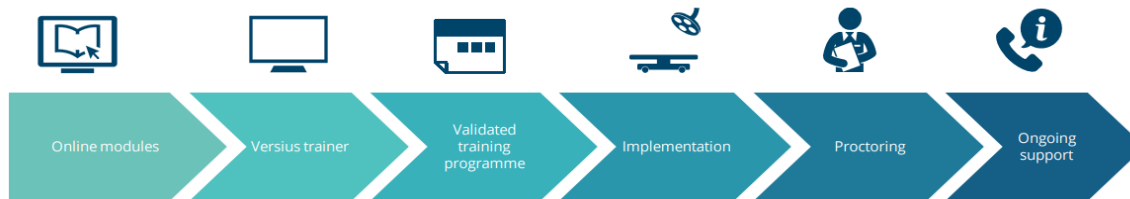
# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: VERSIUS

### Successful clinical introduction



**At home:**

13 online modules  
 Develop familiarity with  
 functionality and  
 capability of Versius  
 Prepares teams for  
 Practical Training  
 Average 10 hours  
 completion time

**In your hospital:**

15 virtual tasks ranging  
 from simple to complex  
 tasks  
 Every console comes  
 with a VT  
 Develop and refine  
 motor and cognitive  
 skills  
 Minimum 5x45hrs

**In the cadaveric lab:**

Practical training for the  
 entire surgical team  
 Equip team to be fully  
 competent operating  
 Versius  
 Provided by dedicated  
 team of CMR Senior  
 Technical Trainers  
 NB: Will not include

**In your hospital:**

Minimum half day OR  
 set up  
 Understand how Versius  
 fits into your OR  
 Working alongside CMR  
 Senior Technical  
 Trainers and Customer  
 Engagement

**In your hospital:**

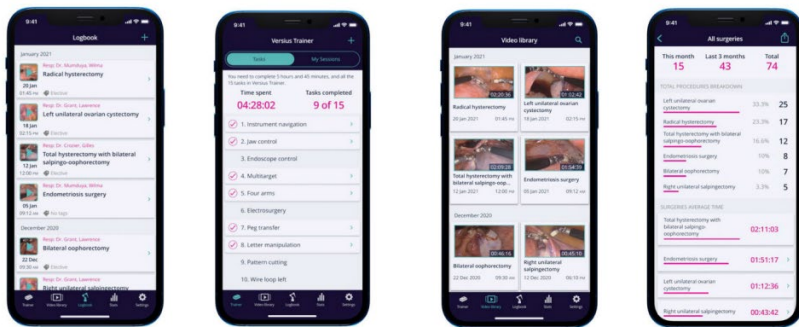
Independent clinicians  
 providing case  
 proctoring  
 Heavily supported by  
 Senior Technical Trainers  
 and Customer  
 Engagement

**In your hospital:**

Continuous product  
 support  
 Ongoing customer  
 service  
 Maintenance and  
 servicing



### The Versius Connect app



A real time  
 logbook

Training  
 Statistics

Video  
 library

View key  
 procedure stats

### The Versius Trainer

#### Digital Surgical Skills Simulator



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: HUGO

Il sistema Hugo™ RAS è stato progettato con i chirurghi di tutto il mondo per rendere possibile di più nella chirurgia robotica assistita.



- Modulare e portatile
- Configurazioni flessibili o spazio della sala operatoria, alla procedura e alle esigenze specifiche del paziente
- Visualizzazione e strumentazione migliorate
- Usa la stessa tecnologia collaudata su open, laparoscopica e RAS.
- Opzione di registrazione video sicura e senza interruzioni
- Analizza e migliora le prestazioni ovunque ti trovi con Touch Surgery™ Enterprise
- Accessibile e scalabile
- Progettato per ridurre il costo totale di proprietà e ottimizzare l'utilizzo del sistema

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: ALF-X



**SOFAR** è conosciuta per aver sviluppato l'avanzato sistema TELELAP ALF-X per interventi chirurgici minimamente invasivi, ora sotto il controllo di TransEnterix

- **Puntamento oculare (3D)**

### Total Laparoscopic (S-LPS) versus TELELAP ALF-X Robotic-Assisted Hysterectomy: A Case-Control Study

F. Fanfani, S. Restaino, C. Rossitto<sup>3</sup>, S. Gueli Alletti, Barbara Costantini, Giorgia Monterossi, Serena Cappuccio, Emanuele Perrone, Giovanni Scambia J. Min. Inv. Gynecol. Sep-Oct 2016;23(6):933-8.

**140 patients**



*Rossitto C, Gueli Alletti S, Romano F et al. Use of robot-specific resources and operating room times: the case of Telelap Alf-X robotic hysterectomy . The International Journal of Medical Robotics and Computer Assisted Surgery. 2016; 12(4): 613-619*

L'analisi dei costi su **81 pazienti** sottoposti a isterectomia robotica Telelap ALF-X. L'analisi del caso base ha mostrato un costo / paziente di € 3391,82. Il nuovo dispositivo robotico richiede un basso consumo di materiali robotici. L'analisi di sensibilità ha mostrato che il fattore di costo più sensibile era l'uso della sala operatoria.

**Impedenza tattile.....!?**



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La chirurgia robotica: il problema costi

### ottimizzazione dei costi:

- crescente domanda di automazione
- migliore decorso p.o.
- calo morbilità, mortalità
- minore riabilitazione nella popolazione geriatrica.....

**ma.....** nel 2020 Statzon dichiara che in chirurgia robotica il mercato globale ammonta a 5,4 miliardi di dollari con una crescita prevista del 13,8% fino al 2028 (pari a 15 MLD US dollars)



**Collegio Italiano dei Chirurghi**

- **Vittorio CREAZZO** (SICCH), Garante
- **Massimo PERACHINO** (AURO), Garante
- **Domenico PITTELLA**, Consigliere giuridico
- **Simonetta DE CHIARA RUFFO**, Consigliere alla comunicazione
- **Elana RISPOLI**, Segreteria nazionale

Sono assenti giustificati: - **Alessandro GRONCHI** (SICO), **Antonio LIMA** (SICP), **Giancarlo D'AMBROSIO** (SICE), **Paolo RUSCITO** (SIOeChCF).

**ORDINE DEL GIORNO**

- Approvazione verbale del 18 ottobre 2021
- Proposta di modello web-app
- Ulteriori specificazioni del contratto ufficio stampa
- Aggiornamento Commissione DRG (Prof. M. Piemonte)
- Costituzione Commissione Pari Opportunità
- Eventuali e varie



**CONSIGLIO DIRETTIVO CIC**  
12 Novembre 2021 ore 18.00 – 19.30  
Riunione in modalità telematica

**AGENAS**  
Agenzia Nazionale per i Servizi Sanitari Regionali

AGENAS ▾ AREE TEMATICHE ▾ RICERCA E SVILUPPO ▾ COMUNICAZIONE ▾ PNRR ▾ PORTALE COVID-19

### CONSULTAZIONE E REVISIONE APERTA

Carissimi Presidenti,  
sono felice di comunicare che il sito **AGENAS** dedicato alla Revisione Aperta tramite Consultazione Pubblica dei **DRG** sarà accessibile da domani al sito <https://www.agenas.gov.it/consultazione-e-revisione-aperta>. Sia la registrazione che il vostro intervento diretto seguono regole intuitive ma necessitano del riferimento dei tabulati già inviati.

Ringrazio il Prof. Domenico Mantoan, Direttore Generale dell'AGENAS, per averci dato questa possibilità d'intervento, l'On. M. Misiti, nostro Segretario, per avere operato con sagacia e determinazione a questo scopo, il Prof. M. Piemonte e l'intera Commissione DRG per il lavoro svolto e tutti voi per quanto avete fatto e saprete fare.

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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.....and LITERATURE??????

8 aprile 2022  
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Presidenti: Gianluigi Greco e Bruno Nardo

XENIA

**Comparison of robot-assisted surgery, laparoscopic-assisted surgery, and open surgery for the treatment of colorectal cancer**

**A network meta-analysis**

Shihou Sheng, PhD<sup>a</sup>, Tiancheng Zhao, PhD<sup>b</sup>, Xu Wang, PhD<sup>c,\*</sup>

Sys rev and Met.: 40 art.; open vs lps vs robotic

12.825 pts

Primary end points:

- operation time,
- estimated blood loss,
- length of hospital stay
- complication,
- mortality
- anastomotic leakage



*only operative time was better for open cases!!!!  
RACS was better for the rest of the items...*

*the present network meta-analysis suggested that RACS might be a better treatment for CRC!!!*

Indian Journal of Surgical Oncology (December 2020) 11(4):633-641  
<https://doi.org/10.1007/s13193-020-01105-7>

ORIGINAL ARTICLE

**Evolution of Robotic Surgery in a Colorectal Cancer Unit in India**

Jitender Rohila<sup>1</sup> • Praveen Kammar<sup>1</sup> • Anadi Pachaury<sup>1</sup> • Ashwin de'Souza<sup>1</sup> • Avanish Saklani<sup>1</sup>

Received: 18 November 2019 / Accepted: 13 May 2020 / Published online: 18 June 2020  
© Indian Association of Surgical Oncology 2020



**Editorial: Advances in and Application of Robotic-Assisted Surgery for Colorectal Cancer**

Po-Jung Chen<sup>1</sup>, Jaw-Yuan Wang<sup>1,2,3,4,5†</sup> and Baoqing Jia<sup>6†</sup>

<sup>1</sup> Division of Colorectal Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, <sup>2</sup> Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, <sup>3</sup> Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, <sup>4</sup> Colorectal Surgery Department, Ministry of Health and Welfare Pingtung Hospital, Pingtung, Taiwan, <sup>5</sup> Pingtung Hospital, Ministry of Health and Welfare, Pingtung, Taiwan, <sup>6</sup> Department of General Surgery, The First Medical Centre, Chinese PLA General Hospital, Beijing, China

**Keywords:** colorectal cancer, robotic surgery, selective ligation of IMA, anastomotic leakage, anal dysfunction management

Editorial on the Research Topic

Advances in and Application of Robotic-Assisted Surgery for Colorectal Cancer

**Better !!!!**

**Equal!!!!**

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Retrospective multi-institutional studies: Ips vs robotic

### Robotic Colorectal Surgery

Poppy Addison, MD<sup>a</sup>, Jennifer L. Agnew, MD<sup>a</sup>, Joseph Martz, MD<sup>a,b,\*</sup>

Surg Clin N Am ■ (2020) ■-■  
<https://doi.org/10.1016/j.suc.2019.12.012>  
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- longer operative times
- lower conversion rate
- shorter length of stay
- less blood loss
- no differences in oncologic outcomes

Table 2  
Summary of studies comparing laparoscopic and robotic colon surgery

First Author, Year	Design	Sample Size	Endpoints	Follow-up (Median)	Conclusion
Bhama et al, <sup>37</sup> 2016	Retrospective	11,477	30-d outcomes	30 d	Longer operative times, decreased length of stay, and decreased conversion rate for robotic
Bhama et al, <sup>37</sup> 2016	Retrospective	4796	Conversion	n/a	Lower conversion rate for robotic
Kang et al, <sup>26</sup> 2016	Retrospective	96 33 open, 43 laparoscopic, 20 robot	Overall survival Disease-free survival Cost	40 mo	Similar outcomes for robotic vs laparoscopic
Tam et al, <sup>39</sup> 2016	Retrospective	2735	Conversion Length of stay	n/a	Lower conversion rate and shorter length of stay for robotic
Widmar et al, <sup>31</sup> 2016	Retrospective	276	Incisional hernia	1 y (robot)	Similar incisional hernia rate
Vasudevan et al, <sup>34</sup> 2015	Retrospective	227	Short-term clinical outcomes Cost	90 d	Similar outcomes
Cleary et al, <sup>35</sup> 2018	Retrospective	2940 1061 open, 1604 lap, 275 robot	Cost Conversion rate	n/a	Higher cost, decreased conversion rate with robotic
Harr et al, <sup>36</sup> 2018	Retrospective	29,172	30-d outcomes	30 d	Fewer conversions, shorter length of stay with robotic
Law et al, <sup>98</sup> 2018	Retrospective	238	Mental and physical workload	n/a	Less mental demand, physical demand and effort in robot group
Lujan et al, <sup>30</sup> 2018	Retrospective	224	Short-term clinical outcomes Incisional hernia	30 mo (robot)	Less blood loss, shorter incisions, longer specimen in the robotic group
Armijo et al, <sup>99</sup> 2019	Retrospective	28	Physical fatigue	n/a	Similar physical fatigue
Polat et al, <sup>25</sup> 2019	Retrospective	378	Radical margins, number of retrieved lymph nodes, locoregional recurrence	15 mo	No difference in oncologic outcomes

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La fluorescenza

### Indocyanine green-enhanced fluorescence to assess bowel perfusion during laparoscopic colorectal resection

Luigi Boni<sup>1</sup> · Giulia David<sup>1</sup> · Gianlorenzo Dionigi<sup>1</sup> · Stefano Rausei<sup>1</sup> ·  
Elisa Cassinotti<sup>1</sup> · Abe Fingerhut<sup>2,3</sup>

Surg Endosc (2016) 30:2736–2742

DOI 10.1007/s00464-015-4540-z

107 patients Ips colorectal surgery ( May 2013 October 2014)

Intraoperative ICG-enhanced fluorescence colonic perfusion after intestinal resection, prior to and after completion of the anastomosis

- right colectomy (n = 40),
- splenic flexure segmental resections (n = 10),
- left colectomy (n = 35)
- anterior resection (n = 22)



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La fluorescenza



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“Re-resection” up to an “adequate” fluorescent part in 4/107 patients (3.7 %)

ICG provides :

real-time evidence of perfusion of the bowel prior to proximal transection, after division of the mesentery and before the completion of the anastomosis in its definitive anatomic position

intraoperative ICG fluorescence might offer the possibility to:

- lower the rate of anastomotic leaks
- reduce the resulting morbidity and mortality rate

**0% leakage**

Results have to be confirmed by larger prospective studies

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## La fluorescenza



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Elisa Cassinotti<sup>1</sup> · Abe Fingerhut<sup>2,3</sup>

Review

Ann Coloproctol 2021;37(3):133-140  
<https://doi.org/10.3393/ac.2021.05.07>



Annals of  
Coloproctology

pISSN 2287-9714 eISSN 2287-9722  
[www.coloproctol.org](http://www.coloproctol.org)

### Multifunctional Indocyanine Green Applications for Fluorescence-Guided Laparoscopic Colorectal Surgery

Gyung Mo Son<sup>1,2,3</sup>, Hong-min Ahn<sup>1</sup>, In Young Lee<sup>2,3</sup>, Gi Won Ha<sup>4</sup>

<sup>1</sup>Department of Surgery, Pusan National University Yangsan Hospital, Yangsan; <sup>2</sup>Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan; <sup>3</sup>Medical Research Center, Pusan National University School of Medicine, Yangsan; <sup>4</sup>Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea

World Journal of  
Gastroenterology

Submit a Manuscript: <https://www.fapublishing.com> World J Gastroenterol 2021 October 14; 27(38): 6374-6386  
DOI: 10.3748/wjg.v27.i38.6374 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**Intraoperative use of indocyanine green fluorescence imaging in  
rectal cancer surgery: The state of the art**

Roberto Peltrini, Mauro Podda, Simone Castiglioni, Maria Michela Di Nuzzo, Michele D'Ambra, Ruggero Lionetti, Maurizio Sodo, Gaetano Luglio, Felice Mucilli, Salomone Di Saverio, Umberto Bracale, Francesco Corcione

The multifunctional ICG are: fluorescent tumor localization, fluorescence lymph node mapping (FLNM), and intraoperative angiography in colorectal cancer surgery can be performed within a single surgery under a laparoscopic or robotic NIR-imaging system.

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La fluorescenza



*Surg Oncol.* 2021 March ; 36: 84–90. doi:10.1016/j.suronc.2020.11.018.

### A Review of Tumor-Specific Fluorescence Guided Surgery for Colorectal Cancer

Hannah M. Hollandsworth, MD<sup>1,2</sup>, Michael A. Turner, MD<sup>1,2</sup>, Robert M. Hoffman, PhD<sup>1,2,3</sup>, Michael Bouvet, MD<sup>1,2,4</sup>

<sup>1</sup>Department of Surgery, University of California San Diego, San Diego CA

<sup>2</sup>Moores Cancer Center, University of California San Diego, San Diego, CA

<sup>3</sup>AntiCancer Inc., San Diego, CA

<sup>4</sup>VA San Diego Healthcare System, San Diego, CA

Mouse studies and clinical studies use of **Fluorescence Guided Surgery** in CRC

- decreased residual tumor
- decrease rates of recurrence

*intraoperative fluorescence imaging can help locate tumor margins, visualize occult micro-metastases and drive surgical decision making!!!*

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## La fluorescenza



Effectiveness and safety of tumor site marking with near-infrared fluorescent clips in colorectal laparoscopic surgery: A case series study

Satoshi Narihiro<sup>a,\*</sup>, Masashi Yoshida<sup>a</sup>, Hironori Ohdaira<sup>a</sup>, Takayuki Sato<sup>b</sup>, Daisuke Suto<sup>c</sup>, Sojun Hoshimoto<sup>a</sup>, Norihiko Suzuki<sup>a</sup>, Rui Marukuchi<sup>a</sup>, Tepei Kamada<sup>a</sup>, Hideyuki Takeuchi<sup>a</sup>, Yutaka Suzuki<sup>a</sup>

<sup>a</sup> Department of Surgery, International University of Health and Welfare Hospital, 537-3, Iguchi, Nasahobara City, Tochigi, 329-2763, Japan

<sup>b</sup> Center for Photodynamic Medicine, Kochi University, Kohasu Oko-cho 185-1, Nankoku, Kochi, 783-8505, Japan

<sup>c</sup> Department of Internal Medicine, International University of Health and Welfare Hospital, 537-3, Iguchi, Nasahobara City, Tochigi, 329-2763, Japan

- 30 patients (May 2019 - October 2019)
- disadvantages of tattoo marking/intraoperative endoscopy-based tumor localization tumor
- site marking with the near-infrared fluorescent clips, ZEOCLIP FS clips (Zeon Med. Co., Ltd., Tokyo, Japan) placed 1–2 days before surgery.

**First report on the case series** using near-infrared fluorescent marking clip

Early results colorectal laparoscopic surgery:

- effectiveness
- safety



**Fluorescent clips could be detected in 94.1% of tumor lesions (lower rectum, obese pts???)**

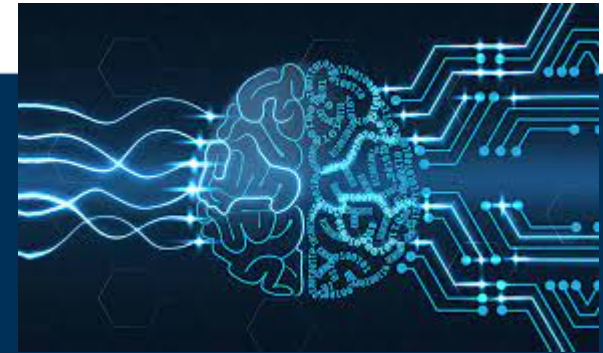


# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

## Artificial intelligence



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- Artificial Intelligence (AI) is a wide-ranging branch of computer science concerned with building smart machines capable of performing tasks that typically require human intelligence.
- AI technology has made great progress, mainly owing to the development of analytical methods such as support vector machines and deep learning.
- continuous learning from data and experience accumulation, the task processing ability of the machine is greatly enhanced.
- AI has been improved through algorithm learning and knowledge management. It has gradually been applied in imaging and pathological diagnosis, disease management, drug research and development and promoting the development of genetics and molecular medicine

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

## Endoscopy



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### Colonoscopy for CRC: Prevention failure

In a typical career of 20K colonoscopies  
a low-detecting colonoscopists may  
fail to prevent up to 80-100 CRCs !!!

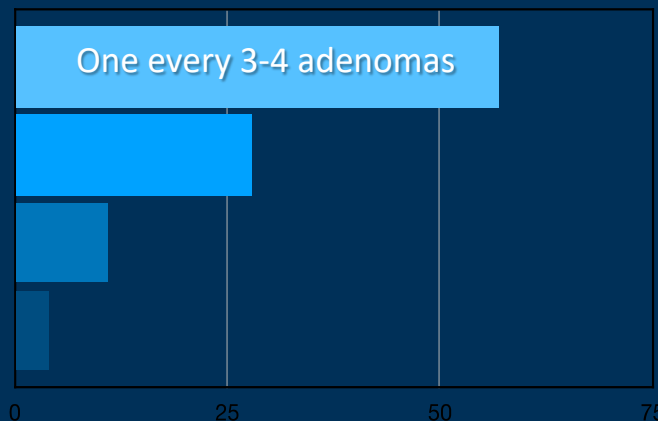


## Prevention failure

### 4 plausible explanations

*Assuming colonoscopy interval was correct based on family history, genetic risk and prior findings on colonoscopy*

- Missed polyps or CRC
- Incomplete polypectomy
- Inaccurate pathology
- *De Novo* progression



Robertson DJ. Gastroenterology 2008

Pabby A. GIE 2010

Hampel. Cancer Prev Res 2011

Pohl H. Clin Gastroenterol Hepatol 2014

Patel SG. Clin Gastroenterol Hepatol 2014

Zhao S. Gastroenterology 2019

Anderson R. Gastroenterology 2020

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

## Artificial intelligence



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In recent years, the application of artificial intelligence in the diagnosis and treatment of colorectal polyps and cancer has increased. These applications include automated polyp detection and classification as well as qualitative and staging diagnosis of colorectal cancer

- Evaluated on 17.574 frames from 18 endoscopic videos, the proposed method could find frames with polyps with an accuracy of 88.6%
- With the advent of deep learning algorithms and significant advances in computer capabilities, more and more AI assistance, some of which may be used in real time during colonoscopy, is now being implemented.



8 aprile 2022 **CONGRESSO REGIONALE SIC e SIPAD INTELLIGENZA ARTIFICIALE, TELEMEDICINA E TECNOLOGIE DIGITALI NELLA CURA DEI PAZIENTI CON TUMORI DELL'APPARATO DIGERENTE** Presidenti: Gianluigi Greco e Bruno Nardo

9 aprile 2022 **TELEMEDICINA E TECNOLOGIE DIGITALI NELLA CURA DEI PAZIENTI CON TUMORI DELL'APPARATO DIGERENTE** Presidenti: Gianluigi Greco e Bruno Nardo

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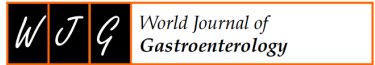
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# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

## Artificial intelligence



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World Journal of Gastroenterology  
 Submit a Manuscript: <https://www.wjgpub.com>  
 World J Gastroenterol 2020; September 14; 26(34): 3090-3100  
 DOI: 10.3746/j.gta.v26.i34.3090 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Potential applications of artificial intelligence in colorectal polyps and cancer: Recent advances and prospects

Ke-Wei Wang, Ming Dong  
 Ke-Wei Wang, Ming Dong, Department of Gastrointestinal Surgery, the First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

### Performance of artificial intelligence in the detection and classification of colorectal polyps

Table 1 Characteristics of studies on artificial intelligence in the detection and classification of colorectal polyps

Ref.	Study type	Algorithm	Imaging modality	Image type	Training set	Testing set	Processing time
Mori <i>et al</i> <sup>[13]</sup>	Pilot study	-	EC	Real-time	-	-	0.3 s/image
Misawa <i>et al</i> <sup>[14]</sup>	Ex vivo	Machine learning: SVM	EC, NBI	Still	979 images (381 non-neoplasms, 598 neoplasms)	100 images (50 non-neoplasms, 50 neoplasms)	0.3 s/image
Kominami <i>et al</i> <sup>[15]</sup>	-	Machine learning: SVM	Colonoscopy, NBI	Real-time	2247 cutout training images from 1262 colorectal lesions	118 images	20 frame/s
Mori <i>et al</i> <sup>[16]</sup>	International web-based trial	Machine learning: SVM	EC	Still	6051 endocytoscopic images	205 small polyps (147 neoplastic and 58 non-neoplastic)	0.2 s/image
Misawa <i>et al</i> <sup>[17]</sup>	Pilot study	Machine learning: SVM	EC, NBI	Still	1661 EC-NBI images (1213 neoplasm images, 448 non-neoplastic images)	124 (19 neoplastic and 105 non-neoplastic)	-
Chen <i>et al</i> <sup>[18]</sup>	Pilot study	Deep neural network	Colonoscopy, magnifying NBI	Still	2157 (1476 neoplastic polyps vs 681 hyperplastic polyps)	284 (96 hyperplastic and 188 neoplastic polyps)	0.45 s/image
Misawa <i>et al</i> <sup>[19]</sup>	Ex vivo	Machine learning	Colonoscopy, WL	Video	411 (105 positive and 306 negative)	135 (50 positive and 85 negative)	-
Shin <i>et al</i> <sup>[20]</sup>	Pilot study	Machine learning	Colonoscopy, WL	Video	1525 (561 polyp patches and 964 normal patches)	366 (196 polyp patches and 170 normal patches)	95 ms/frame
Wang <i>et al</i> <sup>[21]</sup>	Ex vivo	Deep learning	Colonoscopy, WL	Still	5545 (3634 images contained polyps and 1911 images did not contain polyps)	27 113 (5541 images contained polyps and 21572 images did not contain polyps)	-
Kudo <i>et al</i> <sup>[22]</sup>	Pilot study	Texture analysis	EC stained or NBI image	Still	69 142 EC images (43197 stained images and 25945 NBI images)	100 polyps	0.4 s/image
Min <i>et al</i> <sup>[23]</sup>	Pilot study	Gaussian mixture model	Colonoscopy, linked color imaging	Still	139 images of adenomatous polyps and 69 images of non-adenomatous polyps	115 images of adenomatous polyps and 66 images of non-adenomatous polyps	-
Sánchez-Montes <i>et al</i> <sup>[24]</sup>	Pilot study	SVM	Colonoscopy, WL	Still	-	-	-
Horiuchi <i>et al</i> <sup>[25]</sup>	Pilot study	-	Colonoscopy, autofluorescence	Real-time	-	-	-

Ref.	Patients, n	Samples, n	Sensitivity, %	Specificity, %	Accuracy, %	NPV, %	PPV, %
Mori <i>et al</i> <sup>[13]</sup>	152	176	92.0	79.5	89.2	-	-
Misawa <i>et al</i> <sup>[14]</sup>	-	100	84.5	97.6	90.0	82.0	98.0
Kominami <i>et al</i> <sup>[15]</sup>	41	118	95.9	93.3	94.9	93.3	95.9
Mori <i>et al</i> <sup>[16]</sup>	123	205	89.0	88.0	89.0	76.0	95.0
Misawa <i>et al</i> <sup>[17]</sup>	58	64	94.3	71.4	87.8	83.3	89.2
Chen <i>et al</i> <sup>[18]</sup>	193	284	96.3	78.1	90.1	91.5	89.6
Misawa <i>et al</i> <sup>[19]</sup>	73	155	90.0	63.3	76.5	-	-
Shin <i>et al</i> <sup>[20]</sup>	-	366	95.9	95.9	95.9	-	96.4
Wang <i>et al</i> <sup>[21]</sup>	1138	27113	94.4	95.9	-	-	-
Kudo <i>et al</i> <sup>[22]</sup>	89	100	96.9 (stained)	100.0	98.0	94.6	100.0
			96.9 (NBI)	94.3	96.0	94.3	96.9
Min <i>et al</i> <sup>[23]</sup>	91	181	83.3	70.1	78.4	71.2	82.6
Sánchez-Montes <i>et al</i> <sup>[24]</sup>	-	225	92.3	89.2	91.1	87.1	93.6
Horiuchi <i>et al</i> <sup>[25]</sup>	77	258	80.0	95.3	91.5	93.4	85.2
Byrne <i>et al</i> <sup>[26]</sup>	-	106	98.0	83.0	94.0	97.0	90.0

29.451 samples from 14 Authors!!!!

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Artificial Intelligence and Endoscopy

### AI FOR GI MEETINGS CAD (COMPUTER ASSISTED DETECTION)



**GASTROENTEROLOGY,  
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8 aprile 2022 9 aprile 2022

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# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Artificial intelligence

- Recently, a novel AI system (GI-Genius, Medtronic) was reported to have a sensitivity of 99.7% in the detection of colorectal polyps.

- Lo studio, disegnato e coordinato dal prof. Alessandro Repici Direttore del Dipartimento di Gastroenterologia ed Endoscopia digestiva (Humanitas) ha visto la partecipazione degli ospedali Regina Margherita di Roma e Valduce di Como.

- The proportion of false positive frames found from colonoscopy was less than 1% of the total frames.

- Furthermore, the reaction time was shorter using this novel AI system compared with visual inspection by endoscopists in 82% of the cases

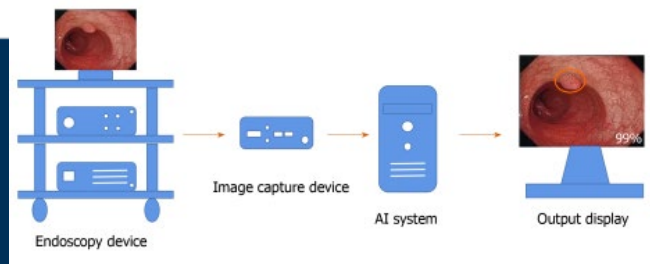


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## Artificial intelligence



- although the results from previous studies appear to be promising, supporting evidence of AI systems applied in colonoscopy is still lacking as most studies were designed retrospectively
- due to the retrospective nature of most studies and the potential selection bias involved, further prospective double-blinded clinical trials are required to confirm the role of AI-assisted colonoscopy in clinical practice
- the establishment of a clinical AI system requires the use of a large amount of clinical data from patients
- the application of medical data also involves protection of patient privacy and ethical issues
- once the information is leaked, it may cause unpredictable consequences
- the safe management of medical data should be a key issue
- only after these problems are appropriately addressed, AI can be used clinically for colorectal diseases

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



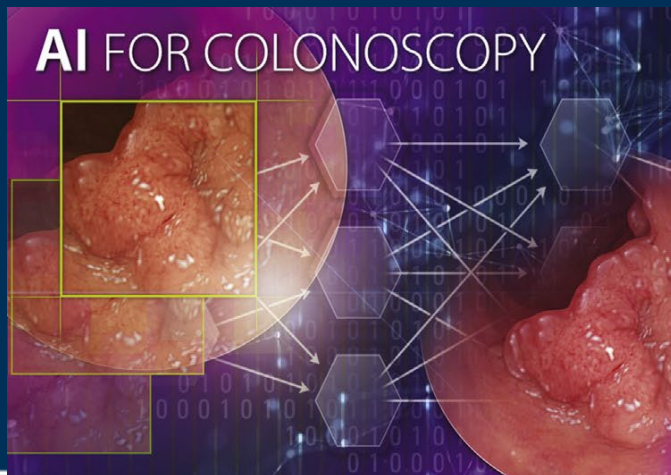
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## Artificial Intelligence and Colonoscopy



CADe (Computer Assisted Detection)

CADx (Computer Assisted Diagnosis)



### Comparative effectiveness of CAD versus control group on ADR

Study / Subgroup	CAD		WL		Weight	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Su et al, 2020	89	308	52	315	11.7%	1.75 [1.29-2.37]	
Wang et al, 2019	151	522	109	536	18.8%	1.42 [1.15-1.76]	
Wang et al, 2020	165	484	134	478	21.7%	1.22 [1.01-1.47]	
Liu et al, 2020	199	508	124	518	22.0%	1.64 [1.36-1.97]	
Repici et al, 2020	187	341	139	344	25.8%	1.36 [1.16-1.59]	
<b>Total (95% CI)</b>		<b>2163</b>		<b>2191</b>	<b>100.0%</b>	<b>1.44 [1.27-1.62]</b>	

Total events: CAD 791, WL 558  
 Heterogeneity:  $Tau^2 = 0.01$ ,  $Chi^2 = 6.91$ ,  $df = 4$  ( $P = 0.14$ );  $I^2 = 42\%$   
 Test for overall effect:  $Z = 5.93$  ( $P < 0.00001$ )

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# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO

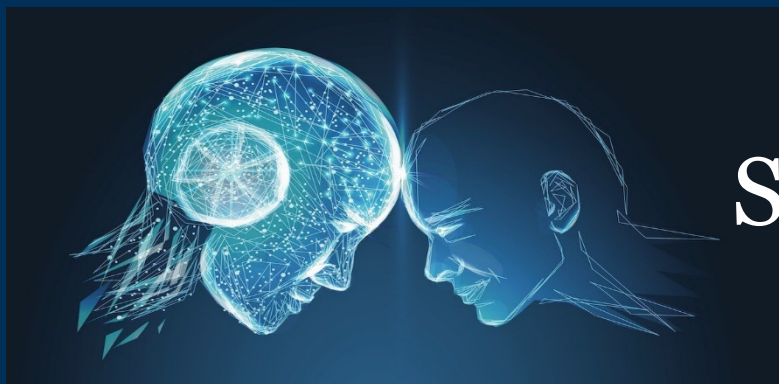


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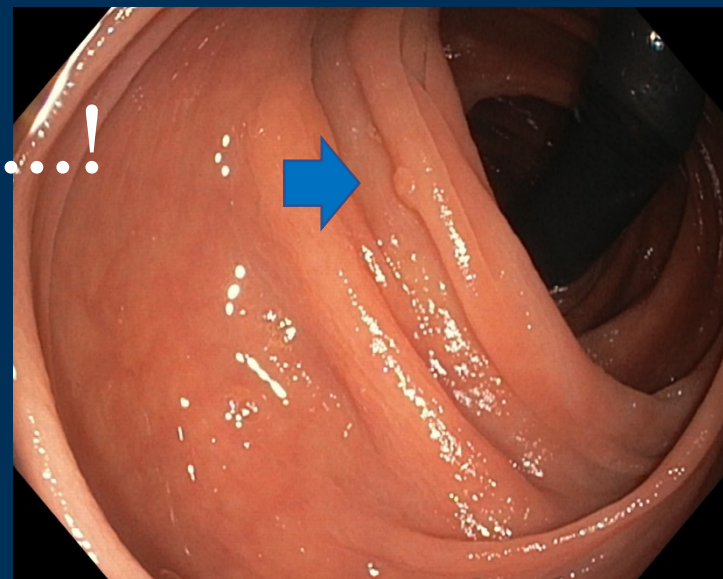
## Artificial Intelligence and Colonoscopy



Artificial Intelligence in Colonoscopy still limited by Human behaviors



STILL.....!



...slow Withdrawal, Twist, Angle and Retroflex

# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Take home messages

La MIS è il presente della chirurgia colo-rettale, la robotica sarà il futuro

- La penetranza della tecnologia è in aumento, da noi al di sotto delle mediane di altri paesi, è rallentata dalla diffidenza ma anche dai costi di gestione
- L'utilizzo della FGS i.o. comporta un minor residuo microscopico del tumore e reduce il tasso di recidiva nei tumori colo-rettali, offre risultati oncologici migliori
- L'utilizzo dell'AI necessita di grandi numeri e studi prospettici per verificarne efficacia
- Studi internazionali multicentrici ne dovranno valutare riproducibilità e stabilità per tutti i tipi di lesioni ed in diversi gruppi di pazienti
- La realtà aumentata comporta una riduzione del carico cognitivo ma anche un aumento dell'efficienza e quindi dei risultati



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



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## Take home messages

L'arrivo del 5G con velocità di 10 GB sec. (latenze 2 sec.) annullerà le latenze nella chirurgia a distanza

Le review dell' ACS-NSQIP e del Michigan Surgical Quality Collaborative Database documentano che la RACS ha tempi operatori più lunghi ed una degenza p.o. significativamente più breve (4.3 gg. vs 5.3 gg), con tassi di conversione minori

Questi grandi numeri consentono di valutare e riconoscere minime differenze tra i diversi gruppi di pazienti anche senza raggiungere una validità statistica

Given the small effect sizes in these studies, robotic surgery should be considered to have clinically equivalent outcomes compared with laparoscopic

L'efficacia della RACS dovrà essere riconsiderata in ulteriori studi prospettici e multicentrici con casistiche ampie e gruppi diversi di pazienti

RACS potrebbe in futuro essere il miglior trattamento per il cancro colo-rettale



# TECNOLOGIA IN CHIRURGIA ONCOLOGICA del COLON-RETTO



*Grazie per l'attenzione!!*

[antonio.crucitti@unicatt.it](mailto:antonio.crucitti@unicatt.it)